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Carcinogenesis, Prevention and Treatment of Colorectal Cancer – State-of-the-Art 2012

February 10 – 11, 2012
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Falk Symposium 182


Munich (Germany)
February 10 – 11, 2012

Scientific Organization:
H. Friess, Munich (Germany)
R.M. Schmid, Munich (Germany)
M. Fried, Zurich (Switzerland)
C.J.H. van de Velde, Leiden (The Netherlands)
CONTENTS

Session I

Histopathological work-up, carcinogenesis and tumor dissemination

Chair:
H. Höfler, Munich
A. Perren, Berne

State-of-the-Art Lecture
Histopathological work-up of biopsies, local excisions and resection specimens in colorectal cancer
P. Quirke, Leeds

Molecular pathological pathways in the development of colorectal cancer (no abstract)
T. Kirchner, Munich

Mechanism of colorectal cancer dissemination in lymph nodes and distant organs (no abstract)
C.A. Klein, Regensburg

MicroRNAs and inflammatory cytokines are associated with diagnosis, prognosis and therapeutic outcome of colon cancer
C.C. Harris, Bethesda

Session II

From bench to bed – Molecular markers for clinical use

Chair:
F.R. Greten, Munich
K.-P. Janssen, Munich

Molecular, blood, and stool tests: Ready to replace colonoscopy?
T.F. Imperiale, Indianapolis

Genetic and epigenetic mutations and targeted therapies in colon cancer – Have we made progress?
S. Tejpar, Leuven
Recurrence score: A multigene assay
D.J. Kerr, Oxford

Session III

Screening- and surveillance programs in low/high risk patients

Chair:
M. Fried, Zurich
B. Göke, Munich

Colorectal cancer screening: Practice guidelines
D.A. Lieberman, Portland

Hereditary colorectal cancer: Identification, surveillance and therapy strategies
J. Burn, Newcastle upon Tyne

Inflammatory bowel disease: Cancer risk, detection and surveillance
G. Rogler, Zurich

Chemoprevention of colorectal cancer with 5-ASA
H. Herfarth, Chapel Hill

Session IV

Screening modalities, endoscopic adenoma detection and therapy

Chair:
M.F. Neurath, Erlangen
R.M. Schmid, Munich

CT and MR colonography – Challenge for endoscopy
D.C. Rockey, Dallas

Endoscopic detection of colorectal adenomas: Standards and sophisticated methods
M. Anders, T. Rösch, Hamburg

Mucosectomy in the colorectum
B. Saunders, London
Session V

Video session – State-of-the-Art colorectal and liver procedures

Chair:
H. Friess, Munich
M. Ghadimi, Göttingen
E. Tiret, Paris

Complete mesocolic excision in right- and left-sided colon cancer
K. Weber, W. Hohenberger, Erlangen 45

Laparoscopic surgery for low rectal cancer
E. Rullier, Bordeaux 46

The Holm’ abdominoperineal resection – Extralevator abdominoperineal excision (ELAPE) for low rectal cancer (video surgery)
G. Jansson-Palmer, T. Holm, Stockholm 47

Accelerated staged hepatectomy (ash) for liver tumors

Session VI

Polypectomy and tailored surgery

Chair:
M. Classen, Reith
C.A. Maurer, Liestal
H. Neuhaus, Düsseldorf

The “difficult” polyp – Pitfalls for endoscopic removal
M. Jung, Mainz 51

Endoscopic therapy options for T1 colon and rectal cancer
A. Meining, Munich 52 – 53

Combined endoscopic-laparoscopic resection
D. Hahnloser, Lausanne 54 – 55

The TEM procedure – Standards and extended indications
Session VII

Management of non-metastatic colorectal cancer (stage I-III)

Chair:
H.J. Buhr, Berlin
K.-W. Jauch, Munich
K.-H. Link, Wiesbaden

Colorectal surgery – What is evidence-based and how should we do it?
E. Tiret, Paris

Bowel obstruction in stenotic colorectal cancer – Stent, stoma or primary resection (no abstract)
P.B. Paty, New York

Sphincter-saving surgery and reconstruction techniques – What is reasonable in the context of cure and functional results? (no abstract)
A. D’Hoore, Leuven

Multivisceral resection for T4 or recurrent colorectal cancer
J. O’Leary, P.R. O’Connell, Dublin

Adjuvant therapy of colon cancer – Present guidelines and future perspectives
W. Schmiegel, Bochum

Session VIII

Multimodal therapy in stage II/III rectal cancer

Chair:
M. Molls, Munich
C.J.H. van de Velde, Leiden
S.D. Wexner, Weston

Neoadjuvant short- or long-term radio-(chemo)therapy: How and who should be treated?
C. Rödel, Frankfurt

Specimen evaluation and histopathologic prognosticators after neoadjuvant therapy in rectal cancer
M. Berho, Weston

Complete response after neoadjuvant therapy in rectal cancer: To operate or not to operate?
S.D. Wexner, Weston
Which patient does not need a preoperative radiation?
M. Büchler, Heidelberg 69

Quality assurance in rectal cancer treatment
C.J.H. van de Velde, Leiden 70

Presentation of poster prizes

Chair:
B. Bashankaev, Moscow; D. Kandioler, Vienna; A. Nissan, Petah Tiqva

Session IX

Management of patients with stage IV colorectal cancer

Chair:
C.-T. Germer, Würzburg
W. Schmiegel, Bochum
A. Tuchmann, Vienna

Synchronous resectable colorectal liver metastases
B. Nordlinger, A. Brouquet, Boulogne 73

Oncological management of irresectable liver metastases
(no abstract)
E. van Cutsem, Leuven

Surgical results after downstaging of initially marginal or non-resectable liver metastases
J. Belghiti, Paris 74

Stage IV colorectal cancer. Hyperthermic intraperitoneal chemoperfusion (HIPEC) in peritoneal carcinomatosis
R. Salazar, P. Barrios, Barcelona 75 – 77

List of Chairpersons, Speakers and Scientific Organizers 79 – 84
1. The sphincter's fate in low lying rectum cancer: A decision analysis
   M. Adamina, S. Wolf, B. Hummel, F. Näf, S. Bischofberger, T. Steffen
   (St. Gallen, CH)

2. Results of intraoperative pelvic hyperthermic chemotherapy for treatment of
   locally advanced rectal carcinoma
   M. Alekseev, E. Rybakov (Moscow, RU)

3. Extranodal non-Hodgkin's lymphomas of gastrointestinal tract
   D. Badea, M. Badea, A. Genunche-Dumitrescu (Craiova, RO)

4. Incidence and clinical evolution of non-Hodgkin lymphoma (NHL) of the colon
   M. Badea, D. Badea, A. Genunche-Dumitrescu, L. Stefan, A. Badea, D. Duta
   (Craiova, RO)

5. The Ann Arbor Staging system versus modified Blackledge Staging system and
   Musoff system in the gastrointestinal lymphoma
   M. Badea, D. Badea, A. Genunche-Dumitrescu, C. Petrica, D. Iordache,
   L. Stefan, D. Duta, A. Badea (Craiova, RO)

6. Capnography improves patient safety during propofol sedation for colonoscopy:
   A randomized, controlled study (ColoCap Study)
   A. Beitz, A. Riphaus, A. Meining, T. Kronshage, C. Geist, S. Wagenpfeil,
   A. Weber, A. Jung, M. Bajbouj, C. Pox, G. Schneider, R.M. Schmid,
   T. Wehrmann, S. von Delius (Bochum, Munich, Wuppertal, Wiesbaden, DE)

7. Are there other indicators of quality of colonoscopy than adenoma detection rate (ADR)?
   M. Benes, P. Drastich, T. Hucl, P. Stirand, P. Wohl, J. Spicak (Prague, CZ)

8. Quality of endoscopic mucosal resection (EMR) at IKEM
   M. Benes, P. Drastich, P. Stirand, P. Wohl, T. Hucl, J. Spicak (Prague, CZ)

9. Compartmental differences of circulating tumor cells in colorectal cancer
   U. Bork, N.N. Rahbari, A. Kircher, E. Seyfarth, T. Niemetz, S. Schölch,
   C. Kahlert, M.W. Büchler, M. Koch, J. Weitz (Heidelberg, DE)

10. Non-invasive screening for colorectal cancer and colon adenomas
    S. Chernyshov, E. Zenkina (Moscow, RU)

11. Is the prevalence of colorectal adenoma higher in patients with gastric
    neoplasm?
12. Gradual loss of functional gap junction within progression from colorectal adenoma to cancer – A shift from membranous CX32 and CX43 expression to cytoplasmic pattern during colorectal carcinogenesis
R. Dereniewicz-Wincewicz, A. Wincewicz, L. Kanczuga-Koda, M. Koda, S. Sulkowski (Kielce, Bialystok, PL)

13. Tubulo-villous colorectal adenocarcinoma vs. mucin and signet-ring cell carcinoma – Is there a prognostic difference?
M. Doß, U. Nitsche, M. Maak, T. Schuster, R. Langer, H. Friess, R. Rosenberg (Munich, DE; Baden, CH)

14. High myeloperoxidase positive cell density in colorectal cancer is an independent favorable prognostic factor

15. Postoperative outcome and long-term survival after laparoscopic assisted right hemicolectomy during the learning curve: A case-matched analysis with open approach
T. Dumitrascu, C. Vasilescu, V. Tomulescu, M. Ionescu, I. Popescu (Bucharest, RO)

16. Risk factors for adverse outcome of emergent colon cancer surgery
S. Faes, A. Schnider, M. Weber (Baden, Zurich, CH)

17. Ulcerative colitis as a risk factor for colorectal cancer
O.V. Fedorova, E. Fedulova, O. Tutina, O. Shumilova (Nizhny Novgorod, RU)

18. IBD: Cytoprotection for the prevention of colorectal cancer
O.V. Fedorova, E. Fedulova, O. Tutina, O. Shumilova (Nizhny Novgorod, RU)

19. HER-2/neu immunoeexpression in colorectal and gastric carcinomas
O. Fratila, T. Ilias, M. Puscasu, R.G. Mihaila (Oradea, Sibiu, RO)

20. Oct4, spliced variant OCT4B1, a novel marker for human colorectal cancer
M. Gazouli, G. Theodoropoulos, M. Roubelakis, A. Vaiopoulos, J. Papailiou, N. Nikiteas, N.P. Anagnou (Athens, GR)

21. Assessment of the local recurrence rates of colorectal cancer after curative resection
A. Genunche-Dumitrescu, D. Badea, M. Badea, P. Mitrut, A. Badea (Craiova, RO)

22. The contribution of major etiologic factors to the risk of colorectal cancer
A. Genunche-Dumitrescu, D. Badea, M. Badea, P. Mitrut (Craiova, RO)

23. Correlation of prognosis and gene expression signatures in colorectal cancer
J. Gröne, L. Lee, J. Lauscher, H.J. Buhr (Berlin, DE)
24. Molecular biomarkers play a major role in the selection of treatment strategies in CRC
   J. Gülden, A. Bogner, M. Joka, K.-W. Jauch, B. Mayer (Munich, DE)

25. A genetic mouse model to identify the role of the immune adapter protein MyD88 in colon cancer
   A. Holtorf, M. Martini, B. Holzmann, K.-P. Janssen (Munich, DE)

26. Colorectal cancer assessment in a group of patients from the western part of Romania
   T. Ilias, O. Fratila, D. Puscasiu (Oradea, RO)

27. Inflammatory response related gene polymorphisms and colorectal cancer
   G. Karamanolis, G. Theodoropoulos, M. Gazouli (Athens, GR)

28. Laparoscopic surgery for rectal cancer
   S. Kathy, D. Tóth, Z. Kincses (Debrecen, HU)

29. CXC-chemokines as crucial immune mediators in colorectal carcinogenesis
   L. Keller, D. Doll, C. Ochs, K.-P. Janssen (Munich, DE)

30. The risk factors of colorectal cancer operations
   Z. Kincses, T. Csobán, S. Kathy, D. Tóth (Debrecen, HU)

31. Importance of the long-term surveillance of patients with ulcerative colitis considering the occurrence of dysplastic changes and colorectal carcinoma
   M. Konecny, V. Prochazka, J. Ehrmann (Olomouc, CZ)

32. Identification of prognostic factors for long-term survival in stage IV colorectal cancer patients

33. Initial results of a randomized controlled trial comparing clinical and pathological downstaging of rectal cancer after preoperative short-course radiotherapy or conventional chemoradiotherapy with delayed surgery
   T. Latkauskas, H. Pauzas, P. Lizdenis, Z. Saladzinskas, A. Tamelis, D. Pavalkis (Kaunas, LT)

34. Radiofrequency-assisted hepatic resections metastases of colorectal cancer
   A. Lavrinenko, V. Kashnikov, E. Rybakov, Y.A. Shelygin (Moscow, RU)

35. Neural invasion is not a prognostic factor in colon cancer due to missing neuro-cancer cell affinity
36. Systematic review and meta-analysis on the effect of preoperative radio(chemo)therapy on long-term functional outcome in rectal cancer patients

37. Tumor targeting of gastrointestinal carcinomas with Shiga toxin B
M. Maak, U. Nitsche, L. Johannes, R. Rosenberg, H. Friess, K.-P. Janssen (Munich, DE; Paris, F; Baden, CH)

38. Colonoscopy screening markedly reduces the occurrence of colon carcinomas and carcinoma-related death
C. Manser, L. Bachmann, J. Brunner, F. Hunold, M. Fried, P. Bauerfeind, U.A. Marbet (Zürich, Glarus, Altdorf, CH)

39. Complex pathology analysis of colorectal cancer in children
N.S. Marenich, A.S. Tertychnyy, D.M. Konovalov, A.G. Talalaev (Moscow, RU)

40. Microsimulation of colorectal cancer screening
B. Misselwitz, C. Manser, L. Biedermann, A. Sonnenberg, P. Bauerfeind (Zürich, CH; Portland, US)

41. A novel mouse model of orthotopic metastatic colon cancer
O. Movadat, A. Wlodarski, N. Wittkopf, M.F. Neurath, C. Becker (Erlangen, Mainz, DE)

42. Immunohistochemical screening of hMLH1 and hMSH2 gene mutations in patients diagnosed with colorectal cancer and microsatellite instability suspicion
F. Muresan, R. Simescu, I. Domsa, R. Buiga, M. Cazacu (Cluj-Napoca, RO)

43. Epiregulin promotes growth of colitis-associated tumors
C. Neufert, C. Becker, M. Waldner, I. Backert, M.F. Neurath (Erlangen, DE)

44. Prediction of prognosis is not improved by the 7th edition of the TNM classification for colorectal cancer

45. Integrative marker analysis and risk assessment in stage II colon cancer

46. Surgical site infection in diabetic patients after colorectal surgery
S. Panidis, D. Paramythiotis, D. Panagiotou, E. Karamanlis, V.N. Papadopoulos, A. Michalopoulos, G. Basdanis (Thessaloniki, GR)

47. Results of salvage abdominoperineal resection after failed chemoradiation therapy for epidermoid anal canal carcinoma: Retrospective analysis at a single institution
48. Gastrointestinal quality of life after laparoscopic-assisted sigmoidectomy for diverticular disease
I. Pasternak, N. Wiedemann, G. Basilicata, G. Melcher (Uster, Liestal, CH)

49. Effect of preoperative radiochemotherapy on lymph node retrieval after resection of rectal cancer
H. Pauzas, T. Latkauskas, P. Lizdenis, Z. Saladzinskas, A. Tamelis, D. Pavalkis (Kaunas, LT)

50. Microvessel density could be strong prognostic marker after radiotherapy in rectal cancer
D. Pavalkis, S. Svagzdys, V. Lesauskaite, Z. Saladzinskas, A. Tamelis (Kaunas, LT)

51. Gasless transanal endosurgery and transanal excision of rectal cancer: Experience from a single center in Moscow
I. Peresada, Y.A. Shelygin, S. Chernyshov (Moscow, RU)

52. Anal sphincter preservation in ultra low rectal cancer surgery – Suffering for the patient or chance to continue customary life?
D. Pikunov, E. Rybakov (Moscow, RU)

53. Adrenal metastases of colorectal carcinomas
C. Pitt, K. Peitgen (Bottrop, DE)

54. Lymph node yield after rectal resection in patients treated with neoadjuvant radiation: A systematic review and meta-analysis
S. Pohle, P. Quentmeier, M. Loos, U. Nitsche, M. Maak, T. Schuster, R. Langer, H. Friess, T. Kocher, R. Rosenberg (Baden, CH; Munich, DE)

55. Preoperative chemoradiotherapy increases sphincter-sparing procedure rate for rectal carcinoma patients
A. Rasulov, Y.A. Shelygin, S. Zhodankina, A. Boiko, I. Drosheeva (Moscow, RU)

56. HLA class I expression in colorectal cancer; prognostic and predictive relevance
M. Reimers, E. Zeestraten, S. Saadatmand, G. Liefers, C.J.H. van de Velde, P.J.K. Kuppen (Leiden, NL)

57. Groin metastases of anal carcinoma: Surgery or chemoradiation
E. Rybakov, S. Chernyshov (Moscow, RU)

58. Primary mixed goblet cell carcinoid/-adenocarcinoma of the cecum with stenotic metastasis in the sigmoid presents as a rare cause of decompensated colon ileus with sigmoid stenosis
A. Sahin, S. Tschuppert, A. Wodzynski, M. Trippel, S. Saravanja, A. Keerl, R. Rosenberg, T. Kocher (Baden, CH)

59. Quality of life after sphincter-preserving rectal cancer resections
J. Scheele, M. Meier, D. Henne-Bruns, M. Kornmann (Ulm, DE)
60. Postoperative complications and risk factors in robotic surgery for rectal cancer  
O. Sgarbura, M. Eftimie, V. Tomulescu, I. Popescu (Bucharest, RO)

61. Screening of irregular bowel movement frequency as functional risk factor of colorectal cancer  
C. Shemerovskii (St. Petersburg, RU)

62. Specific activity of cyclindependent kinase 1 predicts the recurrence of stage II colon cancer  
(Kobe, JP; Leiden, NL; Munich, DE)

63. Colorectal cancer in the region with enormously high occurrence rate: The projection of screening program and clinical practice  

64. The effect of a nationwide screening program on the diagnosis of colorectal cancer (CRC) in a region with an enormously high occurrence  
J. Spicak, M. Benes, T. Hucl, P. Stirand, P. Drastich, O. Urban, V. Nosek  
(Prague, Ostrava, Jablonec nad Nisou, CZ)

65. Surgical reoperations in cases of postoperative sepsis subsequent to the surgical treatment of colorectal cancer  
G. Statescu, A. Statescu, M. Carausu (Iasi, RO)

66. MMP-9 is a strong prognostic survival marker in rectal carcinoma  
S. Svagzdys, V. Lesauskaite, Z. Saladzinskas, A. Tamelis, D. Pavalkis  
(Kaunas, LT)

67. N-acetylcysteine has a powerful dual effect of anti-inflammatory and antioxidant activities resulting in complete improvement of acetic acid induced colitis in rats  

68. Prognostic value and prediction of the presence of KRAS mutation on the basis of combined pathology data of colorectal cancer  
A.S. Tertychnyy, G. De Hertog, X. Sagaert, K. Geboes  
(Moscow, RU; Leuven, BE)

69. Single direct suture of the perineal wound after cylindrical abdominoperineal extirpation of the rectum (Holm-procedure) – An alternative to a Mesh or flap technique  
W. Thasler, M.E. Kreis (Munich, DE)

70. Association of caspase-8 and -9 gene polymorphisms and colorectal cancer susceptibility and prognosis  
G. Theodoropoulos, M. Gazouli, A. Vaiopoulou, N. Nikiteas (Athens, GR)
71. Results of extralevator abdomino-perineal resections for rectal cancer (multicenter study)
P.V. Tsarkov, I.A. Nechay, D.A. Hubezov, V.V. Polovinkin, Y.M. Makeev, A.M. Karachun, I. Tulina, M.A. Danilov, I.S. Tsarkov (Moscow, St. Petersburg, Ryazan, Krasnodar, Balashikha, RU)

72. D3 lymph node dissection in right colon cancer: Too much or just enough?
P.V. Tsarkov, B. Bashankaev, A. Kravchenko, I. Tulina (Moscow, RU)

73. The effectiveness of the multidisciplinary approach in elective surgery of colorectal cancer in elderly patients.
P.V. Tsarkov, V.V. Nikoda, V.I. Stamov, D.R. Markar'yan, I. Tulina (Moscow, RU)

74. Pretherapeutic selection of the most promising drugs for the individual CRC patient using the functional Spheroid Microtumor Model
K. Weiler, L. Rava, C. Ludwig, M. Joka, K.-W. Jauch, I. Funke, B. Mayer (Munich, DE)

75. Erythropoietin receptor expression in colorectal cancer – Immunohistochemical and mRNA studies – In perspective of treatment with recombinant EPO in colorectal cancer-associated anemia
A. Wincewicz, C. Miller, C. Blau, U. Sulkowska, S. Sulkowski (Bialystok, PL; Seattle, US)

76. The role of capsule endoscopy in evaluating and managing small bowel disorders
E. Yoong, K. Padmakumar (Manchester, Bolton, GB)

77. Stomach and colon cancer diagnosis of vitamin B12 and folic acid levels

78. Local recurrence rate in rectal cancer
W. Zaglmair, H. Wundsam, K. Rohregger, G. Pressl, M. Aufschnaiter, K. Emmanuel (Linz, AT)

79. Individual CRC-tumour-ID by combining biomarker profiling and functional 3D drug testing
M. Zoller, J. Gülden, M. Joka, I. Funke, K.-W. Jauch, B. Mayer (Munich, DE)
Session I

Histopathological work-up, carcinogenesis and tumor dissemination
State-of-the-Art Lecture

Histopathological work-up of biopsies, local excisions and resection specimens in colorectal cancer

P. Quirke
St. James’s University Hospital, Leeds, UK

I will describe the currently recommended UK guidelines and their rationale and identify areas for improvement.

Key issues are: Attention to macroscopic pathology with reference to the importance of the planes of surgery in rectal and low rectal cancer and the emerging evidence for colonic cancer. That standardised dissection methods are very important with targeted sampling of not only lymph nodes but other high risk features such as vascular and peritoneal invasion. Proper staging of early cancers is increasing in importance and the current methods have a number of drawbacks. With the increasing use of bowel cancer screening pathologists will face these management decisions more frequently. A common approach to pathological complete response is required and a suggestion will be put forward. The constant changes to TNM need to be brought under control and a more evidence based approach adopted changes. Proforma reporting is very important to allow quality assurance and optimal practice.

The importance of the histopathological phenotype should not be underestimated in the era of genomics, transcriptomics and proteomics.
MicroRNAs and inflammatory cytokines are associated with diagnosis, prognosis and therapeutic outcome of colon cancer

Curtis C. Harris, M.D.
Laboratory of Human Carcinogenesis, NCI, NIH, Bethesda, MD, USA

Colon adenocarcinoma is a leading cause of cancer mortality. Although current adjuvant treatment modalities improve survival for tumor-node-metastasis (TNM) stage III colon cancer patients, whether stage II patients should be given these therapies remains controversial. Some stage II patients will benefit from therapy, but therapy for others will harm quality of life with little therapeutic benefit. Therefore, it is important to develop biomarkers to identify high-risk, early stage patients who may be suitable for therapeutic intervention.

Inflammation plays a key role in tumor initiation, progression, and metastasis. We determined if expression of inflammatory genes in tumors and the surrounding noncancerous tissue can be used as a prognostic biomarker for colon adenocarcinoma. Combining multiple, independent prognostic biomarkers may improve the ability to identify cancer patients at high risk of disease progression and mortality. Therefore, incorporating an additional factor to an inflammatory gene biomarker, i.e., microRNA expression, may serve this purpose.

MicroRNAs are small, non-coding RNA molecules that have shown potential as biomarkers in cancer. Expression levels of microRNAs are altered in all cancers that have been studied. Specific microRNAs can modulate tumor progression in mouse models, showing their potential to be “drivers” in carcinogenesis. We recently reported that patients with tumors expressing high levels of an oncogenic microRNA, miR-21, have worse survival prognosis for stage II or stage III colon adenocarcinoma, showing its potential as a prognostic biomarker for colon cancer. Because miR-21 expression is linked to inflammation and both miR-21 and inflammatory gene expression are linked to colon cancer, combining inflammatory gene biomarkers with miR-21 can improve their clinical utility.
Session II

From bench to bed – Molecular markers for clinical use
Molecular, blood, and stool tests: Ready to replace colonoscopy?

Thomas F. Imperiale, MD
Indiana University Medical Center, Indianapolis, IN, USA

Identifying an accurate, reliable, affordable, and acceptable non-invasive screening test for colorectal cancer (CRC) would greatly facilitate population screening. This session will discuss the status of non-invasive screening tests for CRC.

The highest quality evidence for non-invasive screening exists for guaiac-based fecal occult blood testing (gFOBT), for which the incidence and mortality benefits are modest. Fecal immunochemical testing (FIT) offers better sensitivity and comparable specificity. Cross-sectional studies comparing gFOBT and FIT suggest that FIT provides higher detection of advanced neoplasia. Modeling studies favor FIT over gFOBT with respect to effectiveness and cost-effectiveness. A myriad of studies report the performance of fecal-based and blood based genetic and protein-based biomarkers; the studies differ in patient population, marker selection, and assay methods. Several markers and panels or markers are promising, although nearly all studies amount to proof-of-concept or early assessment of discrimination by new markers and/or assay methods on small sets of referred patients rather than validation of markers using optimal assays in a screening setting.

In the absence of long-term randomized trials like the ones for gFOBT, adoption of the non-invasive tests will require: 1) cross-sectional data on test characteristics obtained from the screening setting, where CRC prevalence is low and the full spectrum of colorectal findings exists; 2) from modeling studies, estimates of cumulative risks, benefits, and cost-effectiveness. Test adoption will ultimately depend on test performance (sensitivity, specificity) in the screening setting, availability, affordability, and user appeal. At this time, there is no non-invasive substitute for the currently-recommended screening tests. FIT should replace gFOBT wherever gFOBT is being used for screening.
Genetic and epigenetic mutations and targeted therapies in colon cancer – Have we made progress?

S. Tejpar
Digestive Oncology Unit, University Ziekenhuis Gasthuisberg, Leuven, Belgium

Colorectal cancer is very heterogeneous disease, possibly even different diseases hitting the same organ. This has huge implications for clinical practice and the development of anti cancer drugs in this disease. Only two biomarkers for colorectal cancer are currently sufficiently validated for the clinic. Efforts to find genetic patterns that distinguish between tumors with good or poor prognosis or between patients who do or don’t responder to various therapies are proceeding slowly but steadily. We will discuss various approaches, using cell lines, mouse models, patient tumors that can provide key information. Key examples will be discussed, such as the identification of response signatures to EGFR inhibitors in colon cancer, or understanding the role of oncogenic BRAF in this disease, to highlight both gains and gaps in our knowledge. We will also discuss how lack of knowledge hampers current drug development and the challenges faced by both pharma and academia in developing successful trials, balancing biomarker identification and validation in this disease.
Recurrence score: A multigene assay

David J. Kerr
Nuffield Department of Clinical and Laboratory Sciences, University of Oxford, UK

The Quasar Trial randomized 3239 patients after apparently curative resection of colon or rectal cancer, 90% of whom had stage II disease, to receive chemotherapy with fluorouracil and folinic acid (n = 1622) or to observation (n = 1617). After a median follow up of 5.5 years, it was obvious that chemotherapy reduced recurrence rates by around 20% and improved overall survival in absolute terms by around 3.6% (p = 0.04). This was the first study to show a survival benefit for stage II colorectal cancer patients and mandates an informed discussion with all stage II patients on the pros and cons of this well tolerated chemotherapy. Anecdotally, elderly patients usually decline treatment and the subgroup of younger (< 65 years) subjects are more likely to consider treatment. There have been attempts to use pseudo-scientific post hoc subgroup analysis to define “bad prognostic criteria”, based on pathological criteria e.g. T4, lympho-vascular invasion, grade etc. The problem with this approach is that the studies linking these variables to outcome are retrospective, mostly underpowered, sometimes conflicting and never subject to quality controlled prospective validation studies. Given the quality of the data base, it is therefore a continuing source of puzzlement that these factors have gained traction in clinical guidelines or treatment algorithms for stage II disease.

A transatlantic collaboration between QUASAR and NSABP Trials Groups, Cleveland Clinic (CC) and Genomic Health, was formed to test whether RNA expression levels might improve risk assessment and treatment decisions in stage II colon cancer. Recurrence-free interval (RFI), disease free survival (DFS) and overall survival (OS) were analyzed using Cox regression. In the 4 developmental studies (NSABP and CC) (total n = 1851), gene expression was quantitated by RT-PCR from 30 µm, manually microdissected, fixed, paraffin-embedded primary colon cancer tissue. Multivariate analysis, of 761 candidate genes, in the context of stage, grade, nodes examined and MSI status, yielded 18 genes (7 prognostic genes, 6 predictive genes, 5 reference genes) and separate prognostic Recurrence Score (RS) and predictive Treatment Score (TS) signatures. In the QUASAR validation study, tumor blocks were collected from 68% of pts and RT-PCR was performed in 1436 stage II colon cancer pts with median follow-up of 6.6 yrs. In the primary analysis of relapse free interval, the RS predicted recurrence risk (HR/25 units = 1.58, 95% CI: 1.15–2.15; p = 0.004), disease free (p = 0.01) and overall survival (p = 0.04). Recurrence risk increased with increasing RS, with 3 year recurrences of 12%, 18% and 22% in the pre-defined low, intermediate and high recurrence risk groups. In multivariate analyses, RS retained prognostic significance (p = 0.008) independent of mismatch repair (MMR), T stage, nodes examined, grade, and lymphovascular invasion. However, the TS was not validated as a predictor of chemotherapy benefit (p = 0.19), which may relate to the fact that the development studies did not have a sufficiently large population of patients randomized between chemotherapy and control arms.

We believe that the continuous RS provides individualised assessment of recurrence risk and will have the greatest clinical utility when used in conjunction with T stage, and Mismatch Repair Status, particularly for the majority of patients (70%) for whom those markers are uninformative. A prognostic algorithm has been developed separating T4 and MMR-Deficient tumours – the bad and good prognostic groups for whom most
clinicians would be likely to recommend chemo (T4) or avoid it (MMR-D), with the RS being used to further stratify risk in T3 MMR-P tumours into relatively low/high risk of recurrence. Although the proportional benefits of chemotherapy are similar in all prognostic groups, the absolute benefits range from 1% (clinically trivial?) to 5% (clinically worthwhile?), allowing treatment considerations to be discussed with well-informed patients.
Session III

Screening- and surveillance programs in low/high risk patients
Colorectal cancer screening: Practice guidelines

David A. Lieberman, M.D.
Division of Gastroenterology, Oregon Health & Science University, Portland, OR, USA

Colorectal cancer (CRC) screening has been demonstrated to reduce both incidence and mortality of CRC. There are several different screening options, each with potential benefits and some limitations.

1. Fecal blood testing
   These tests are primarily early cancer detection tests, but may also identify patients with important cancer precursor lesions. Effectiveness has been shown in randomized trials of guaiac-based tests. New data strongly suggest that fecal immunochemical testing is more sensitive for detection of cancer and advanced adenomas, and is preferred in many countries.

2. Structural exams of the colon.
   These tests may detect both early cancer and cancer precursor lesions, and are more likely to result in cancer prevention than fecal blood tests.
   a. Flexible sigmoidoscopy
      New randomized controlled studies from UK and Italy both demonstrate significant reduction in both incidence and mortality, but benefit is limited to the distal colon.
   b. Colonoscopy
      Case-control and data-base studies have shown significant reductions in incidence and mortality in patients who receive colonoscopy. There are no randomized trials. Benefits in the proximal colon have been questioned in recent studies.
   c. Imaging
      CT colonography may be as sensitive for detection of polyps greater than 10 mm as optical colonoscopy. There are concerns about radiation exposure, rate of extra-intestinal findings and detection of “flat” polyps.

New forms of screening using stool DNA, capsule endoscopy and serum testing for genetic mutations are still in evolution, though proof of principle studies have been published.
Lynch syndrome is an autosomal dominant disorder which results from a pathological variant in one of the mismatch repair genes. It is characterised by the development of a range of different malignancies, particularly of the colon and endometrium. The hallmark microsatellite instability reflects frameshift mutations which generate novel peptides which in turn generate an immune response. This provides part of the explanation for the relatively good prognosis. There remains doubt over the variation in response to therapy of sporadic and hereditary mismatch repair deficient cancers but recent results have established the importance of early identification of gene carriers in order to make available chemoprevention.

There is extensive evidence over 2 decades that aspirin is protective against cancer. The CAPP2 randomised controlled trial demonstrated among 1009 gene carriers a clear effect in Lynch syndrome. After a delay of about 4 years the rate of new cancers was reduced by 60%. The dose used in CAPP2 was 600 mg per day of enteric coated aspirin. There was no reported excess of adverse events in the trial, but it is to be expected that that a recommendation to take 600 mg aspirin on a lifelong basis will result in a substantial cumulative burden of adverse events. This makes it essential that a full cost benefit analysis is carried out and every effort made to reduce the iatrogenic burden. Recent meta-analyses of follow-up via cancer registry records of participants in early aspirin vascular trials suggest that regular use of low dose aspirin may be equally beneficial in cancer prevention. Low dose aspirin has never been trialled in a recognised Lynch syndrome population. CAPP3 will establish whether a low dose aspirin regime is preferable to the proven dose of 600 mg per day in this high risk cohort. Suppression of frame shift peptide antibody development will be tested as a new biomarker of prevention while new nanowire technology will be applied to broaden the scope for case identification.
Inflammatory bowel disease: Cancer risk, detection and surveillance

Gerhard Rogler
Klinik für Gastroenterologie und Hepatologie, Universitätsspital Zürich, Zürcher Zentrum für Integrative Humanphysiologie (ZIHP), Zurich, Switzerland

It is well-known that there is an increased risk for patients with ulcerative colitis (UC) to develop colorectal cancer (CRC). The risk is significantly increased as compared to the total population after disease duration of 8 to 10 years in patients with pancolitis and after 15 years in patients with left-sided UC (1). The severity of the disease, the duration of mucosal inflammation and the presence of a primary sclerosing cholangitis (PSC) are further risk factors (2). A similarly increased risk has been described for patients with Crohn's colitis (3). The outcome of CRC in patients with inflammatory bowel disease (IBD) is poorer as compared to non-IBD patients (4).

Several retrospective studies indicated that surveillance colonoscopy reduces the risk for UC patients to die from CRC (5). A Swedish case control study indicates that surveillance colonoscopy reduces the mortality risk to less than one third (relative risk 0.29) (6).

Due to this knowledge, surveillance colonoscopies starting after 8 years or 15 years after diagnosis and thereafter every two years are recommended for UC patients (7). They are intended to find intraepithelial neoplasias (IEN) before a definitive colorectal cancer has developed. Based on older data and publications it has been suggested (i.e. in the respective guidelines) that the likelihood to discover intraepithelial neoplasias rises with the number of the biopsies taken during endoscopies. Newer techniques such as chromoendoscopy have been suggested to improve the diagnostic yield (8). However, IEN detection rates of up to 30–40% found by chromoendoscopy are surprisingly high and hard to interpret. An ongoing study presently investigates whether high resolution endoscopy and narrow band imaging allow only to biopsy suspect lesions and avoid the time consuming 56 random biopsies that are recommended in the respective guidelines at present.

References:


Chemoprevention of colorectal cancer with 5-ASA

Hans Herfarth
Department of Medicine, University of North Carolina, Chapel Hill, NC, USA

Patients with ulcerative colitis are at increased risk for developing colorectal cancer. The risk for colorectal cancer in patients with ulcerative colitis depends on the duration, the extent and severity of the disease, age at the onset of the disease, the existence of a coincident primary sclerosing cholangitis as well as backwash ileitis and a positive family history of colorectal carcinoma. In patients with Crohn’s disease, chronic and extensive inflammation of the colon is probably also an important risk factor for the development of colorectal cancer.

Chemoprevention of colorectal carcinoma
Several retrospective studies have demonstrated that preparations containing 5-aminosalicylic acid (5-ASA) exerts a protective effect against the development of colonic dysplasia or colorectal cancer in patients with ulcerative colitis. This protective effect has been extensively analyzed for nonsteroidal anti-inflammatory drugs (NSAID’s) such as diclofenac or acetylsalicylic acid (aspirin) and is probably pathophysiologically a result, amongst other factors, of a decrease of prostaglandin biosynthesis. Cyclooxygenase (COX), which consists of two isoforms, is a key enzyme in the synthesis of prostaglandins and eicosanoids from arachidonic acid. Studies on human and induced colorectal cancers in animal models demonstrate both an increase in the activity of COX-2 and in the concentration of prostaglandin E2 in such tumors. Moreover, in addition to the inhibition of prostaglandin synthesis, a direct proapoptotic and antiproliferative effect of NSAIDs, which is mediated by the inhibition of the transcription factor NF-κB, as well as the inhibition of the peroxisome-proliferation-associated receptors (PPARs) are further protective mechanisms against colorectal cancer.

A meta-analysis of the effect of 5-ASA use and colorectal cancer and dysplasia risk in patients with ulcerative colitis demonstrated a protective association between use of 5-ASA and colorectal cancer with an odds ration of 0.51 (95% confidence interval: 0.38–0.69). However a dose > 1.2 g/day 5-ASA is probably required to achieve this protective effect. There are also some studies demonstrating no chemoprotective effect. To better evaluate the effects of 5-ASA for the chemoprevention of colorectal cancer in patients with ulcerative colitis prospective studies are clearly needed. However, for a meaningful trial design large numbers of patients would have to be included over a long period of time, which make these studies unlikely to occur. Nevertheless, according to the current analysis of all available retrospective data, continuous maintenance therapy of patients with ulcerative colitis with preparations containing 5-ASA probably represents an important option to prevent the development of colorectal cancer.
References:


Session IV

Screening modalities, endoscopic adenoma detection and therapy
CT and MR colonography – Challenge for endoscopy

Don C. Rockey  
Division of Digestive and Liver Diseases, University of Texas Southwestern Medical Center, Dallas, TX 75390-8887, USA

Computed tomographic (CT) and magnetic resonance (MR) colonography, are two of the newest modalities proposed as a method to screen the colon for cancer. They have a number of attractive features consistent with their use a potentially important colon cancer screening examinations. Currently, they require preparation of the colon, but are noninvasive and do not appear to cause major complications. However, a limitation of the exams is that if abnormalities are identified, subjects will require (therapeutic) colonoscopy. A number of controversial areas exist.

A major endeavor in the field has been to investigate the sensitivity of imaging studies compared to colonoscopy. Early reports of CT colonography (CTC) typically involved smaller populations at high risk for colorectal pathology and used single-row scanners. Later studies generally demonstrated improved detection sensitivity for polypoid lesions, but notably, continued to reveal wide variation in results. The now well publicized multicenter trials with variable results are well imprinted in everyone’s minds, but recent data suggest in particular that CTC is as sensitive as colonoscopy for detection of large lesions. There have been many more studies of CTC than MR colonography, and studies to date suggest that CTC is more sensitive than MR colonography.

Imaging studies readily detect extracolonic lesions of varying importance (calcifications, gallstones, hernias, bone lesions, abdominal aortic aneurysms, benign and malignant tumors). The cost of evaluation of these potentially important (or clinically meaningless) lesions remains a major issue.

Training and assurance of quality is perhaps one of the most critical aspects in the entire field. Data continue to emerge with regard to how much training is required, and moreover, whether individuals with different types of backgrounds can be adequately trained to read imaging studies.

CTC and MR colonography have rapidly matured, but many questions remain about their use. These include a myriad of issues related to all of the topics highlighted above. However, perhaps the most important – and difficult – question is that given the current climate, how should these imaging tests be integrated into current colon cancer screening programs?

Addresses for correspondence:

Don C. Rockey, M.D.  
Professor and Chief, Division of Digestive and Liver Diseases  
University of Texas Southwestern Medical Center  
Dallas, TX 75390-8887, USA  
E-Mail: don.rockey@utsouthwestern.edu
Endoscopic detection of colorectal adenomas: Standards and sophisticated methods

Mario Anders, Thommas Rösch
Interdisciplinary Endoscopy, University Clinics of Hamburg-Eppendorf, Hamburg, Germany

Colorectal cancer represents one of the leading malignancies worldwide. Timely endoscopic detection and removal of its precursor lesions results in a decrease of colon cancer related death. However, miss rates in adenoma detection up to 26% underline the need for high compliance to basic measures and further improvement in methodology and technology. Basic parameters affecting adenoma detection rates include sufficient training and awareness of the endoscopist, use of high-definition endoscopes, careful examination behind folds, cleansing the colon wall, accurate distention of the colon, and adequate withdrawal time. Advanced imaging techniques, introduced to further improve adenoma detection have yielded mixed results though. Those include of wide-angle colonoscopes, cap-assisted colonoscopy, and retroscopic methods which however, may make colonoscopy more complicated. Chromoendoscopy either by topically applied dyes or “virtual” has been suggested to enhance the detection of colonic neoplasia yet, studies on patients with average cancer risk failed to reproduce promising initial results. Similarly, autofluorescence did not enhance the diagnostic yield in screening a population at average risk, nonetheless, may be useful in patients at higher cancer risk. Recently, technical feasibility of molecular imaging employing “biomarkers” has been demonstrated yet needs further evaluation. Newest developments, employing lightscattering spectroscopy, suggest the existence of a “field effect” of colonic carcinogenesis and may enable detection of earliest neoplastic events and distant adenomas even when applied to normal-appearing mucosa. Upon confirmation, these technologies may lead to a substantial change in patient management and risk stratification.
Mucosectomy in the colorectum

B. Saunders
Wolfson Unit for Endoscopy, St. Mark’s Hospital, London, UK

**Mucosectomy in the colorectum**

Dr. Brian Saunders
Wolfson Unit for Endoscopy
St. Mark’s Hospital

**EMR: BASIC PRINCIPLES**

- ACCESS IS EVERYTHING!
- 1. straight scope position
- 2. wash & suction fluid/residue
- 3. insufflate and/or change patient position
- 4. rotate scope to get polyp at 5 o’clock
- 5. get assistance holding the scope shaft
- 6. get diathermy set up & ready to go before snaring polyp

DO YOUR OWN CUTTING
NEVER IGNORE PATIENT DISCOMFORT

---

**EMR/ESD: room set-up**

- protective clothing
- patient monitoring
- at least 2 assistants
- adequate time
- accessories laid out and ready
- familiarity with diathermy unit
- “endoscopic check list”
- team work, calm and efficient

**Assessing endoscopic resectability**

- morphology (Paris classification)
- mucosal deformity/size
- pit pattern (dye/NBI)
- ulceration
- feel
- “non-lifting sign”

Non-lifting sign indicates deep submucosal invasion...

sensitivity 63%, specificity 100%

*Magron 1993, Jue 1994*

---

**Sessile and flat lesions**

**Endoscopic Mucosal Resection**

- anywhere in colon
- lesions > 2cm
- take normal mucosa at edge
- superficial sm plane
- inject - cut - inject

- endocut 120W, effect 2

**Piecemeal-EMR**

ERBE ICC200
**Piecemeal EMR: risk of late recurrence at 1 year in 4.4%**

*Khasab and Rex. Gastrointestinal Endoscopy 2009*

*follow up at 3 and 12 months after resection*

---

**severe submucosal scarring endoscopic mucosal ablation (EMA)**

- spiral snare
- hyaluronate
- APC “melt effect”

*Tsiamoulos & Saunders 2011 GIE (in Press)*

---

**Predictors of failure to eradicate polyp at first EMR attempt (20%)**

*DDW 2010 abstract*

*Australian, prospective, multi-centre EMR database, 314 lesions median size 3.4cm*

<table>
<thead>
<tr>
<th>OR</th>
<th>Failure to lift</th>
<th>Involving ileo-caecal valve</th>
<th>Previous polypectomy attempt</th>
<th>Use of thermal ablation</th>
<th>Difficult position</th>
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<tbody>
<tr>
<td>5.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.9</td>
<td></td>
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<td>2.6</td>
<td></td>
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<tr>
<td>1.9</td>
<td></td>
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**TEM vs EMR**

<table>
<thead>
<tr>
<th></th>
<th>TEM (n = 215)</th>
<th>EMR (n = 73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure time [mean]</td>
<td>70 (±4.56)</td>
<td>73 (±3.95)</td>
</tr>
<tr>
<td>LOS (days)</td>
<td>3 (0-44)</td>
<td>0</td>
</tr>
<tr>
<td>Post-op complications</td>
<td>12 (24%)</td>
<td>9 (12%)</td>
</tr>
<tr>
<td>Reoperation rates</td>
<td>12 (9%)</td>
<td>0</td>
</tr>
<tr>
<td>Readmission</td>
<td>19 (9%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>LOS readmission (days)</td>
<td>6 (2-26)</td>
<td>1 (1-1)</td>
</tr>
<tr>
<td>Remnantadenoma on F/U</td>
<td>16 (19%)</td>
<td>16 (28%)</td>
</tr>
</tbody>
</table>

*Barendse R. Colorectal Dis 2011 Oct 24. [Epub ahead of print]*

---

**Systematic review of ER vs TEMS for large rectal adenomas**

*Barendse RM et al. Endoscopy 2011*

- 1980 - 2009
- 20 EMR studies & 48 TEMS

<table>
<thead>
<tr>
<th></th>
<th>EMR</th>
<th>TEMS</th>
</tr>
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<tbody>
<tr>
<td>Mean polyp size</td>
<td>31mm</td>
<td>37mm</td>
</tr>
<tr>
<td>Early recurrence</td>
<td>11.2%</td>
<td>5.4%</td>
</tr>
<tr>
<td>Late recurrence</td>
<td>1.5%</td>
<td>3%</td>
</tr>
<tr>
<td>Complications</td>
<td>3.8%</td>
<td>13%</td>
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<tr>
<td>Re-intervention</td>
<td>0.2%</td>
<td>3.1%</td>
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<tr>
<td>Hospitalisation</td>
<td>2.2 days</td>
<td>4.4 days</td>
</tr>
<tr>
<td>Mortality</td>
<td>0.46%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

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**Endoscopic Submucosal Dissection**

- deeper submucosal resection
- definitive histology
- cure for early, superficial sm cancer
Histological criteria for conservative management of early rectal cancer

- Very small risk (<3%) of lymph node metastasis
- Well/moderately well differentiated tumour
- Sm invasion depth <1mm
- No lymphatic/vascular invasion
- No tumour budding

Ueno et al Gastroenterology 2004

ESD: training

- Animal lab
- Porcine stomach and colon
- Expert guidance
- Team approach
- Only experienced EMR endoscopists

- Mucosal incision
- Submucosal dissection

ESD in colorectum

- Perforation rates of 5-10% (but clipping usually successful)
- Need for in-patient stay
- Long procedure times
- Technically difficult
- MORE EXPENSIVE THAN EMR

Procedural bleeding can occur frequently!

Hemostatic forces
(soft coagulation 60-80W)
Endoclips
APC

ESD: Japanese clinical practice


- 200 consecutive cases
- Median follow up 24 months
- En-bloc resection: 91.5%
- En-bloc histologically(R0): 70.5%
- Recurrence: 1.8%

BUT...

- Perforation: 11
- Significant bleeding: 2
- Major Complication: 6.5%

Colorectal ESD

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>en-bloc resection rate</th>
<th>perforation rate</th>
<th>post-op bleeding rate</th>
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<tbody>
<tr>
<td>Fujihira</td>
<td>200</td>
<td>91.5%</td>
<td>10.4%</td>
<td>1.0%</td>
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<tr>
<td>Saito</td>
<td>200</td>
<td>83.0%</td>
<td>9.0%</td>
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<tr>
<td>Tanaka</td>
<td>70</td>
<td>80.0%</td>
<td>10.0%</td>
<td>1.4%</td>
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<td>Tamegai</td>
<td>71</td>
<td>89.6%</td>
<td>1.4%</td>
<td>0.0%</td>
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<tr>
<td>Toyonaga</td>
<td>361</td>
<td>89.2%</td>
<td>2.2%</td>
<td>0.8%</td>
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<td>Yoshida</td>
<td>119</td>
<td>81.2%</td>
<td>7.5%</td>
<td>1.6%</td>
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<td>Zhou</td>
<td>74</td>
<td>93.2%</td>
<td>8.1%</td>
<td>1.3%</td>
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<tr>
<td>Takeuchi</td>
<td>50</td>
<td>94.0%</td>
<td>2.0%</td>
<td>12.0%</td>
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<tr>
<td>Isomoto</td>
<td>292</td>
<td>90.1%</td>
<td>8.2%</td>
<td>0.7%</td>
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</table>


Hybrid ESD, P-EMR

- Circumferential lesion isolation
- Partial dissection
- Clear lateral margins
- Large piece EMR

Bourke et al. Endoscopy 2010; 42: 400-4
Colorectal lesions

Benign lesions  Sm1 cancer  Sm 2/3 and all T2

- lifting characteristics
- surface pattern - NBI
- EUS/MRI

ER  TEMS or Surgical resection

P-EMR, Hybrid  ESD
Session V

Video session – State-of-the-Art colorectal and liver procedures
Complete mesocolic excision in right- and left-sided colon cancer

K. Weber, W. Hohenberger
Chirurgische Klinik und Poliklinik, Universitätsklinikum Erlangen, Erlangen, Germany

The presented videos demonstrate the principle of “complete mesocolic excision” (CME) in the surgical treatment of colon cancer.

Analogous to the “total mesorectal excision” (TME) in rectal cancer surgery the preparation is performed strictly in embryological planes. The division of the supplying arteries of the tumor bearing colon segment is done right at their origin (at the superior mesenteric artery or the aorta, respectively). This technique leads to a specimen with maximized lymph node harvest and intact mesocolic fasciae enveloping potential tumor deposits.

Performing this CME principle in our department we observe cancer-related 5-year survival rates of 85% in stage I–III colon carcinomas and of 80% in stage III tumors alone.
Laparoscopic surgery for low rectal cancer

Eric Rullier
Department of Surgery, University of Bordeaux – Saint-Andre Hospital, Bordeaux, France

Aim: Feasibility and oncologic outcome of laparoscopic surgery with sphincter preservation in low rectal cancer is not established. We aimed to evaluate the results of laparoscopic conservative rectal excision for low rectal cancer.

Methods: Between 2000 and 2010, patients operated by laparoscopic conservative rectal excision for low rectal cancer ≤ 6 cm from anal verge were included. Patients with T3–T4 or N+ disease had preoperative radiochemotherapy. Surgery was performed 6 weeks after irradiation by two surgeons specialized in TME and laparoscopic surgery. It included high ligation of IMA, splenic flexure mobilization and total mesorectal excision with preservation of the pelvic anatomic nerves. Dissection was performed by using ultrasonic or monopolar instruments. The perineal step included rectal transection, transanal rectal specimen extraction and side-to-end hand-sewn coloanal anastomosis. A loop ileostomy was systematically used for 2 months. End points were mortality, morbidity, pathological data, recurrence and survival.

Results: Of 527 laparoscopic procedures for rectal cancer, 220 patients had a coloanal anastomosis for low rectal cancer. There were 139 males and 81 females, with a median age of 64 years (range 20–90). The tumor was located at 4 cm (range 1–6) from the anal verge. They were 39 uT1T2, 175 uT3 and 6 uT4; 130 were uN+. Preoperative radiochemotherapy was used in 192 patients (87%). A conventional Park’s coloanal anastomosis was performed in 68 patients (31%), whereas intersphincteric resection was necessary in 152 patients (69%). Conversion to open procedure occurred in 15% of the cases. Mortality was 0.5% (1 of 220) and surgical morbidity (Dindo III-V) was 18%. Pathological tumour stage was 0 in 17 cases, I in 87 cases, II in 43 cases and III in 73 cases. The distal margin (median 15 mm) and the circumferential margin (median 4 mm) were negative in respectively 93% and 87% of the cases. A complete microscopic excision, i.e. R0 resection, was achieved in 185 cases (84%). With a median follow-up of 43 months (range 1–135), the rate of local and distant recurrence were respectively 4% and 21%. There was no perineal or port side recurrence. The 5-year overall and disease-free survival were 86% and 70%, respectively.

Conclusion: Laparoscopic surgery with sphincter preservation for low rectal cancer is technically and oncologically safe, if performed by a team specialized in both TME and laparoscopic surgery. It offers the advantages of the mini invasive surgery with the same oncologic results than open surgery.
The Holm’ abdominoperineal resection – Extralevator abdomino-perineal excision (ELAPE) for low rectal cancer (video surgery)

Gabriella Jansson-Palmer, Torbjörn Holm
Department of Colorectal Surgery, Karolinska University Hospital Solna, Stockholm, Sweden

Background: Conventional abdominoperineal excision (APE) for low rectal cancer is frequently associated with intraoperative tumor perforation, positive circumferential margins (CRM+) and wound infections. The outcome after APE has a higher degree of local recurrences and a worse overall survival compared to low anterior resection (LAR) of higher rectal cancer operated with TME surgery. The aim of this study was to report the results after the introduction of extra-levator abdominoperineal excision (ELAPE) in a consecutive prospective study from a single colorectal unit.

Patients and methods: Between 2000 and August 2011, 151 patients with low rectal cancer were treated at the Karolinska University Hospital with ELAPE. The principal difference in the surgical procedure from a conventional APE is that the mesorectum is not dissected of the levator muscles and the perineal dissection is done in a prone position where the levator muscle is dissected en bloc with the anus and lower rectum.

Results: Of the 151 patients 90 (60%) had a preoperative assessed locally advanced rectal cancer (T4). R0 was obtained in 128; R1 in 23. Fourteen perforation of the bowel close to the tumor occurred. Involved circumferential margin was observed in 29 (19%). During the follow up of 109 patients 2000–2009 (11–122 months) seven local recurrences occurred and 37 patients received disseminated disease.

Conclusions: The surgical technique of ELAPE in low rectal cancer has a low risk for bowel perforation and CRM involvement. Local recurrences occurred less frequently in this study compared to previous reported studies of outcome after APE surgery.
Accelerated staged hepatectomy (ash) for liver tumors

Erik Schadde, Stefan Breitenstein, Mickael Lesurtel, Michelle de Oliveira, Christoph Soll, Pierre-Alain Clavien
Swiss HPB Center, University of Zurich Hospital, University of Zurich, Switzerland

Radical resection with free margins is the only way to achieve cure in metastasis colorectal cancer to the liver. Frequently both liver lobes are involved with disease and the feasibility of radical resection depends on the volume and quality of the future liver remnant.

The video demonstrates a new technique of staged hepatectomy to perform radical resections by using the regenerative capacity of the liver. In a first step the lobe with less metastases is cleared from metastatic disease through non-anatomic resections. At the same operation a transection of the hepatic parenchyma is performed to separate the lobe with remaining metastases from the cleaned lobe. The lobe with remaining metastases then undergoes portal vein ligation to induce hypertrophy in the cleaned lobe. After only one week this combination of parenchymal transection and portal vein ligation results in massive hypertrophy of the cleaned lobe allowing for removal of the diseased lobe, and thereby all remaining disease, within one week. The video demonstrates the technique as developed by the Zurich group in several cases

This accelerated staged hepatectomy allows the diseased liver to work as an auxiliary liver in the phase after the first operation and induces more hypertrophy than any procedure described in the past.
Session VI

Polypectomy and tailored surgery
The “difficult” polyp – Pitfalls for endoscopic removal

M. Jung
Klinik für Innere Medizin und Gastroenterologie, Katholische Klinikum Mainz, St. Hildegardis-Krankenhaus, Mainz, Germany

Adenomatous polyps are early neoplasias of colorectal cancer (sequence adenoma-carcinoma). The majority of adenomas or of early invasive cancers (T1sm1) can be resected by endoscopy.

Endoscopic resection techniques include the classic loop polypectomy, endoscopic mucosectomy with preceding lifting of the (almost flat) lesion, endoscopic submucosal dissection (ESD) and TMR (transanal microsurgical resection), an alternative to ESD in the rectum.

Endoscopic polyp removal should always aim to resect the lesion in “one piece” and should avoid, when ever possible, “piece meal resection”. One piece polypectomy is the basis for a precise histopathological analysis and to prove complete removal of the lesion.

Preceding injection of saline solution into the submucosa to lift the targeted polyp is a therapeutic modality to remove even flat and flat depressed adenoma. In addition a positive lifting sign is regarded as a criterion of lower superficial malignancy. Lifting of a polyp can be negatively influenced by an already advanced cancer (T1 sm3/T2) into the deep parts of the submucosa as well as by scars and connective tissue in the upper two layers of the colorectal wall. Hence a negative lifting sign may lead to incorrect macroscopic evaluation of the lesion before removal.

Endoscopic submucosal dissection is mostly performed in large laterally spreading tumors in the rectum and in the pre anal region (LST-G.-NG). The technique has a relatively long learning curve and is somewhat time consuming.

A “difficult polyp” may be characterized by
1. the size (> 3 cm), pedunculated or sessile (Ip/Is)
2. by the morphological type (classification of Paris 2003), in particular the flat type II lesions IIa-c flat, flat depressed; laterally spreading tumors (LST) and the large sessile serrated lesions (SSA)
3. the difficult assessment of the grade of malignancy before removal (e.g. DALM, sporadic adenoma, colitis carcinoma)

Chromoendoscopy (with indigo carmine) represents an adequate method to differentiate advanced flat and depressed Typ II lesions from those with lower malignancy and to better identify DALMs and sporadic adenomas in patients with long lasting ulcerative colitis. To reduce the risk of resection (haemorrhage 0–6%; perforation 0.2%; Münchener Studie, Endoscopy 2005); the application of haemoclips to visible vessels or injection of adrenaline (1:10,000) in the polyp stalk before removal are methods to prevent bleeding.

In case of immediate bleeding, the treatment with haemoclips, injection (adrenaline or fibrin sealant) or by endoloop are efficacious to manage this problem. Small perforations can be treated at once by the application of haemoclips, or, in case of larger or difficult leakages by Ovesco clips to avoid surgical interventions.
Endoscopic therapy options for T1 colon and rectal cancer

Alexander Meining
2nd Medical Department, Klinikum rechts der Isar, Technical University of Munich, Germany

Colonoscopy has become the standard for colon cancer screening and prevention. Polypectomy is meanwhile routinely performed and even lesions of several centimeters can be safely removed. Lesions with high-grade dysplasia and intramucosal cancer have no risk for lymphovascular spread and thus complete endoscopic removal is considered curative. However, submucosal cancer is identified in a small portion of polyps removed by endoscopic polypectomy. Although variable, there is about a 10% risk of lymph node metastasis and, thus, there is a risk for unfavorable outcome (local recurrence, lymph node, and distant metastasis) with sole endoscopic removal. Thus, many of these patients are referred for oncologic surgery in hopes of removing the entire cancer, thereby preventing unfavorable outcomes.

In contrast, it has also been reported that the risk of an unfavorable outcome is below the probability of post-operative mortality if cancers invade only the upper third of the submucosal layer, and if histology shows cancers that are well-differentiated with no signs of invasion of lymphatic vessels. Nevertheless, most of these data derive from the surgical literature with optimal histopathological assessment and intraoperative detection or exclusion of lymph node metastasis. Hence, it can be difficult to transfer these data to the solely endoscopically treated patients directing further management (follow-up or oncological surgery) after endoscopic therapy of colorectal cancers in stage T1. There are very sparse data on long-term follow-up of patients with cancers treated solely endoscopically. It appears that invasion of lymphatic vessels with tumor cells can be regarded the strongest predictor for a bad outcome, whereas venous vessel involvement and even tumor grading appears to be less relevant as previously thought. Furthermore, it is also crucial that tumors should be completely resected.

In essence, there is only one way to find out the future risk for unfavorable outcome of T1 colorectal cancer: removal of the lesion with an intent to cure and a proper and detailed histologic assessment. The importance of polyp or lesion assessment before the resection cannot be emphasized enough because the configuration and additional features (e.g., surface patterns, wall stiffness) provide great detail regarding the nature of the lesion and the cancer stage. A non-lifting sign with injection of fluid is important to identify those lesions with deeper invasion. High-frequency endoscopic ultrasound or new MRI-techniques may add information for selecting patients for endoscopic resection rather than surgery. If available, proper techniques (such as endoscopic submucosal dissection – ESD) should be used for the removal of the lesion in a well-planned fashion, aiming for complete removal of the cancer to reduce local recurrence. The complicated polyps are best referred to a tertiary referral center for better outcome because a failed removal at the first attempt makes the complete removal extremely difficult, resulting in less effective removal of the polyp.

Hence, in summary, we need to use pathologic and endoscopical data to recommend surgery until we have more accurate predictors for the risk of recurrence. Finally, apart from these histologic and endoscopic aspects, the decision of which therapy is ideal depends on many individual factors including patient’s age, personal wish, and general
health condition. Risks and benefits should be carefully balanced. The patient should be informed of the potential consequences of a more aggressive approach (postoperative morbidity and mortality) but should also be aware that solely follow-up can be sometimes frustrating because of the persisting uncertainty of lymph node metastasis or tumor relapse.
Combined endoscopic-laparoscopic resection

Dieter Hahnloser
Department of Visceral Surgery, University Hospital Lausanne, Switzerland

Colon polyps are generally removed endoscopically with low complication rates. Postpolypectomy perforation of the colon secondary to either manipulation or cautery effects occur in 0.1% to 3.0%. In case or perforation surgical intervention is frequently required with its associated morbidity. A polyp larger than 2.5 cm in diameter was shown to be significantly correlated with malignant transformation in 34% and polyps larger than 3 cm can be completely excised only in 67–75% of the cases, thus questioning the endoscopic approach. In addition, a variety of “difficult polyps” are not accessible for colonoscopic removal because of their size, broad base, or difficult location (impossible to see the polyp’s base, polyps behind mucosal folds or in tortuous colonic segments).

Combined endoscopic-laparoscopic resection allows a more “aggressive” endoscopic polypectomy. Laparoscopy can help to maneuver the colon into a more favorable position for endoscopic polypectomy and to examine the serosal surface to rule out perforation after polypectomy. This allows the endoscopist to be more “aggressive” during polypectomy, ensuring complete resection of the polyp. In addition, if the polyp cannot be removed endoscopically, or if perforation occurs, or if the frozen section demonstrates invasive cancer patients can be treated with laparoscopic surgery during the same intervention.

Several studies have described this combined approach. In a series of 251 polyps most of the polyps resected were located in the right (59%) and in the rectosigmoid colon (19%). Mean operating time was 96 minutes with an estimated blood loss of 46 ml. Serosal suturing was necessary in 10%. The mean hospital stay was 1.1 day with a return to full activity after 2 days (range 1–10 days). Intraoperative complications were very rare and were mainly dependent on the need for a surgical segmental or an anatomical resection. Main indications for surgical resection were the finding of a cancerous polyp in 6–13%. Successful endoscopic polypectomy could be performed in 11 out of 19 patients (58%), suggesting that many endocopicall “unresetable” polyps can, in fact, be resected endoscopically. Table 1 gives an overview of the success rates, failure rates with the need for surgical resections.

Table 1: Success rates and need for surgery

<table>
<thead>
<tr>
<th>Author</th>
<th>N patients</th>
<th>Successful endoscopic resection</th>
<th>Cancer in final histology</th>
<th>Laparoscopic resection needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Winter (2009)^3</td>
<td>38</td>
<td>21%</td>
<td>13%</td>
<td>74%</td>
</tr>
<tr>
<td>Wilhelm (2009)^2</td>
<td>146</td>
<td>82%</td>
<td>11%</td>
<td>18%</td>
</tr>
<tr>
<td>Franklin (2009)^1</td>
<td>160</td>
<td>91%</td>
<td>7%</td>
<td>14%</td>
</tr>
<tr>
<td>Agrawal (2010)^4</td>
<td>19</td>
<td>26%</td>
<td>6%</td>
<td>31%</td>
</tr>
<tr>
<td>Yan (2011)^5</td>
<td>23</td>
<td>87%</td>
<td>0%</td>
<td>13%</td>
</tr>
<tr>
<td>Wood (2011)^6</td>
<td>13</td>
<td>77%</td>
<td>8%</td>
<td>23%</td>
</tr>
</tbody>
</table>
Combined endoscopic-laparoscopic is feasible, safe, and has a high success rate. Malignant lesions can be treated laparoscopically during the same operation, avoiding the need for a second procedure, and with good long-term oncologic outcome.

References:


Address for correspondence:

Prof. Dr. Dieter Hahnloser
EBSQ Coloproctology
Department of Visceral Surgery
University Hospital Lausanne
Rue du Bugnon 46
1011 Lausanne, Switzerland
E-Mail: dieter.hahnloser@chuv.ch
The TEM procedure – Standards and extended indications

Colorectal Surgery Unit, Department of Abdominal Surgery and Transplantation, Department of Gastroenterology and of Pathology, Cliniques Universitaires Saint-Luc, 10, Avenue Hippocrate, 1200 Brussels, Belgium

Transanal endoscopic microsurgery (TEM) is a minimally invasive surgical technique originally designed for local excision of benign rectal tumors via the anus, thus avoiding conventional open surgery. Problems emerge when preoperatively benign polyps reveal neoplastic foci or invasive adenocarcinoma, which leads to the question of further radical resection. In these cases TEM allows an excisional biopsy of the resection scar using the full thickness technique. In our series, the absence of remaining neoplastic tissue in the biopsy led to endoscopic and radiological follow-up of these patients. In the presence of residual T1 tumor, full thickness biopsy allows precise sm staging and consequently to adapt therapeutic strategy. A growing number of authors report about TEM resection of small rectal cancer although this indication remains controversial regarding the oncological outcome. Two randomized control trials comparing anterior resection and TEM conclude in the absence of adverse oncological outcome for T1–T2 tumors and consider the technique to be valid for the treatment of this niche of patients. However, one must remain careful though, as TEM does neglect the nodal risk ranging between 10% and 34% for pT1 and around 19% to 30% for pT2 tumors. Nevertheless, TEM is a safe and effective technique for the resection of adenomas. It is suitable for the treatment of highly selected small T1 adenocarcinomas and serves in further staging after endoscopic resection of polyps with malignant foci. Even if controversy remains, it appears that TEM is suitable for selected group of patients i.e. favorable T1 cancers.
Session VII

Management of non-metastatic colorectal cancer (stage I-III)
Colorectal surgery – What is evidence-based and how should we do it?

Prof. Emmanuel Tiret
Hôpital Saint-Antoine, AP-HP, 184, rue du Faubourg Saint-Antoine, 75012 Paris, France, E-Mail: emmanuel.tiret@sat.aphp.fr

Evidence based medicine was first defined by Sackett as the conscientious, explicit and judicious use of the current best evidence in making decisions about the care of individual patients. This requires good quality studies with a high level of proof. However these studies are often lacking in colorectal surgery. Nevertheless the topics on which there is general agreement will be discussed.

There is now good evidence that the laparoscopic approach is at least equivalent in oncological terms to the conventional open approach in colonic surgery. However, the question remains unanswered for rectal cancer surgery which is technically more demanding. Although there are no randomized studies, the introduction of total mesorectal excision for rectal cancer has achieved a major reduction in local recurrence and has been adopted as the gold standard by all colorectal surgeons. It is now being discussed to extend this concept to colonic cancer surgery. The different types of reconstruction in sphincter preserving surgery which achieve a better functional result than straight anastomosis, including colonic pouch, transverse coloplasty and side to end anastomosis will be discussed. The benefit of temporary faecal diversion in low anastomosis has now been demonstrated with a good level of evidence. The technique of abdominoperineal resection has evolved in the last years and now aims at obtaining a cylindrical specimen, which has resulted in a significant reduction of the local recurrence rate. In early rectal cancer, the technique of local resection has been improved by the introduction of transanal endoscopic microsurgery (TEM procedure).
Multivisceral resection for T4 or recurrent colorectal cancer

J. O’Leary, P.R. O’Connell
Surgical Professorial Unit, St. Vincent’s University Hospital and UCD School of Medicine and Medical Sciences, Dublin, Ireland

Background: Approximately 10% of patients with colorectal cancer have locally advanced disease with peritoneal involvement (T4a) or invasion of adjacent organs (T4b) at the time of diagnosis. Of patients who undergo resection with curative intent, between 7% and 33% develop isolated loco-regional recurrences. R0 surgical excision is potentially curative.

Methods: We reviewed the literature relating to multivisceral resection for T4 or recurrent colorectal cancer.

Results: Comprehensive staging to identify the local and systemic extent of disease is essential to determine resectability and patient suitability for a curative approach. PET scan and pelvic MRI (rectal) staging and a coordinated multispecialty input to neoadjuvant treatment, multivisceral surgical resection, reconstruction and adjuvant chemotherapy are essential. Intra-operative radiotherapy and hyperthermic intra-peritoneal chemotherapy may have a role in selected patients. R0 resection can achieve five year local control rates for primary locally advanced and recurrent colorectal cancer of up to 89% and 38% respectively and overall 5 year survival up to 66% and 25% respectively.

Conclusion: An aggressive surgical strategy as part of a multimodal strategy in the treatment of locally advanced or recurrent colorectal cancer in the absence of incurable metastatic disease affords the best prospect for long-term survival in selected patients.
Adjuvant therapy of colon cancer – Present guidelines and future perspectives

Wolff Schmiegel
Medizinische Universitätsklinik, Knappschaftskrankenhaus, Ruhr-Universität Bochum, Germany

Colorectal cancer is one of the leading cancer entities and represents the second leading cause of cancer deaths for men and women in the Western World. While approximately 25% of patients first present with distant metastases, more than 50% of patients are diagnosed within the curative UICC stages II and III, which may qualify for adjuvant therapy. Adjuvant treatment should start approximately four weeks after curative R0-resection of the primary cancer and the locoregional lymph nodes and should last for six months.

Adjuvant treatment of colon cancer is recommended according to the initial UICC stage of the patient and certain risk factors. If lymph nodes are afflicted (UICC stage III) combination chemotherapy with oxaliplatin and fluoropyrimidines (5-FU or capecitabine) should be administered (evidence level 1a, recommendation level A) following data from the French MOSAIC study (André, J Clin Oncol. 2009). If patients do not qualify for combination treatment because of comorbidities then monotherapy with fluoropyrimidines should be given, preferring capecitabine over 5-FU (Twelves, N Engl J Med. 2005). When patients are diagnosed with stage II cancer the recommendation for adjuvant therapy depends on the presence of certain risk factors such as T4-category, emergency surgery, perforation, not enough lymph nodes examined (less than 12). Then, patients should receive adjuvant chemotherapy with fluoropyrimidines. However, none of these risk factors has been validated prospectively. Also, their predictive value is unclear. The analysis of the MOSAIC study and recent presentations from the NSABP group confirm that oxaliplatin should not be added in stage II cancer even if risk factors are present (Yothers, ASCO. 2011). If patients are diagnosed within stage II without the above mentioned risk factors then fluoropyrimidines may be given according to the results of the QUASAR study (Lancet. 2007). The absolute survival benefit amounts to 3.6%. In contrast, the ASCO guidelines do not recommend chemotherapy for stage II patients without risk factors (Benson, J Clin Oncol. 2004). ESMO recommendations will be published early next year.

While clinical and histopathological risk factors are well established in adjuvant therapy of colon cancer we still don’t know which molecular make-up of the tumor benefits particularly from adjuvant treatment, mainly in patients with stage II cancers. Recently, the presence of a high microsatellite instability has proven to be associated with a particular beneficial prognosis mainly in patients with stage II colon cancer (Roth, ASCO. 2009). Therefore, some authors recommend to include the test on microsatellite instability into the treatment algorithm for stage II patients. Although, there is probably no predictive value to the marker, the absolute benefit of adjuvant therapy is only approximately 2% since overall prognosis is excellent. Other markers such as muational status of k-ras or b-raf or CpG island methylation has been discussed in various publications. However, no definite conclusion can be drawn for clinical practice. Lastly, novel gene signatures have been identified such as oncotype DX or Coloprint. These signatures may well differentiate between good and bad prognosis mainly in stage II cancers. However, they do not show predictive value for fluoropyrimidine based therapy. Furthermore, ongoing prospective evaluation of the signatures will show their role in clinical practice for patients with stage II colon cancer.
Session VIII

Multimodal therapy in stage II/III rectal cancer
Neoadjuvant short- or long-term radio-(chemo)therapy: How and who should be treated?

Claus Rödel
Department of Radiotherapy and Oncology, University of Frankfurt, Germany

There are two general approaches to preoperative radiotherapy in rectal cancer: Short-course (25 Gy in 5 fractions) radiation with immediate surgery and long-course 5-fluorouracil-based chemoradiotherapy (CRT, 50.4 Gy in 28 fractions) with surgery scheduled 6–8 weeks thereafter. While it is clear that downsizing and downstaging effects are more pronounced with long-course CRT and delayed surgery, a Polish randomized trial and, more recently, an Australian phase III trial demonstrated no significant differences in long-term oncologic outcomes and late toxicity rates between both preoperative concepts. Ongoing studies currently address short-course preoperative RT with a longer interval to surgery (Stockholm III trial), and short-course RT with sequential combination chemotherapy in patients with synchronous distant metastasis or primarily unresectable rectal cancer. With respect to the long-course CRT approach, newer generation chemotherapeutics, such as oral fluoropyrimidines, oxaliplatin, irinotecan as well as molecularly targeted agents (cetuximab, bevacizumab) have been tested within phase I-III studies, both as induction/adjuvant chemotherapy as well as during concomitant CRT. Evidently, the monolithic approaches, established by studies more than a decade ago, to either apply the same schedule of preoperative 5-FU-based CRT to all patients with TNM stage II/III rectal cancer or to give preoperative short-course RT for all patients with resectable rectal cancer irrespective of tumor stage and location, need to be questioned. The inclusion of different multimodal treatments into the surgical oncological concept, adapted to the tumor location and stage and to individual patient’s risk factors is mandatory. Clearly, future developments will aim at identifying and selecting patients for the ideal treatment alternatives. Thus, clinicopathological and molecular features as well as accurate preoperative imaging will take an important and integrative part in multimodality treatment of rectal cancer.
Specimen evaluation and histopathologic prognosticators after neoadjuvant therapy in rectal cancer

M. Berho
Department of Pathology, Cleveland Clinic Florida, Weston, FL, USA

The introduction of the total mesorectal excision technique for the treatment of rectal cancer has resulted in a significant reduction in local recurrence. The basis of the surgical procedure is the en bloc resection of rectum and its surrounding adipose tissue. Thorough pathological examination is a key step in predicting prognosis as well as electing the right post surgical treatment for patients with rectal cancer. Pathological examination of TME specimens consists of several steps:

1. **Assessment of the quality of the mesorectum**
   The integrity of the mesorectum is critical to prevent local recurrence. Evaluation of the quality of the mesorectum is done by the pathologist by examination of the surgical specimen. Assessment of the mesorectum usually follows the following classification:
   - Complete (grade 3): Intact mesorectum, with only minor irregularities. No defects deeper than 5 mm. Smooth circumferential margin. No coning
   - Nearly complete (grade 2): Moderate bulk to mesorectum but irregularities on mesorectal surface. Some coning
   - Incomplete (grade 3): Little bulk to mesorectum with defects down to muscularis propria and/or very irregular circumferential margin

2. **Determination of the pathological TN stage**
   Tumor stage is still the strongest predictor of survival in colorectal cancer therefore accurate evaluation of the depth of tumor invasion and the presence of metastatic disease into the mesorectal lymph nodes is of utmost importance. Within the pathological TN stage, the status of the lymph nodes, positive or negative for malignancy, is crucial to predict prognosis in patients with colorectal cancer. The number of dissected lymph nodes depends on several variables one of which is the effort that pathologists apply in finding lymph nodes in the mesorectum. In the era of neoadjuvant chemoradiation for the treatment of rectal cancer lymph node yield from the mesorectum has significantly decreased (see syllabus on lymph nodes and neoadjuvant therapy).

3. **Evaluation of the margins of resection:**
   One of the most important tasks that the pathologist has is the assessment of the margins of resection. Several publications have demonstrated that the status of the circumferential (radial) margin of resection is one of the most important factors that influence local and distant recurrence. A positive circumferential margin of resection is defined as the presence of tumor at or at least less than 1 mm from the margin.

4. **Quantification of tumor response to neoadjuvant chemoradiotherapy (CRT)**
   As mentioned above most patients with advanced rectal cancer are offered neoadjuvant chemoradiotherapy. Although clinical evaluation of tumor response to preoperative CRT either by radiological means or endoscopy offer a preliminary assessment of tumor response, histopathological evaluation of the area of the tumor...
is the gold standard for evaluation of residual disease. Several grading systems have been proposed to document the different degrees of tumor response. The College of American Pathologists recommends the following system

- No residual tumor identified, grade 0
- Moderate response, minimal residual disease, grade
- Minimal response, grade 2
- No definitive response, grade 3
Complete response after neoadjuvant therapy in rectal cancer: To operate or not to operate?

Steven D. Wexner, M.D.
Cleveland Clinic Florida, Department of Colorectal Surgery, Weston, FL 33331, USA

Optimal management of the patient with distal rectal carcinoma in whom a complete response is achieved with neoadjuvant therapy continues to be intensely debated. The balance between avoidance of a major resection, albeit as a minimally invasive procedure but possibly with a permanent stoma, and nonoperative observation is a very difficult one. The former option has the obvious advantage of allowing complete accurate staging and therefore directing the potential addition of postoperative chemotherapy. However it has the clear disadvantage of introducing the morbidity of a major operation as well as inducing potential functional compromise following a coloanal anastomosis, often including an intersphincteric dissection. The latter option has the obvious advantage of avoiding the potential adverse sequelae of resection surgery but the profound disadvantage of the lack of definitive tumor staging. The fact that approximately one-third of patients who have had a complete response to neoadjuvant therapy have tumor deposits in either the mesorectum and/or lymph nodes is alarming. This lecture will present a the data reflecting both the results of expectant observation and the issue of occult extraluminal tumor deposits following a local complete response. The presentation will also discuss the results of salvage surgery after failure of expectant observation and the results of functional failure and morbidity following major resectional surgery.

Address for correspondence:

Steven D. Wexner, MD, FACS, FRCS, FRCS (Ed)
Chief Academic Officer and Emeritus Chief of Staff Cleveland Clinic Florida
Professor & Chair, Department of Colorectal Surgery
Associate Dean for Academic Affairs Florida Atlantic University College of Medicine
Affiliate Dean for Clinical Education Florida International University College of Medicine
2950 Cleveland Clinic Blvd.
Weston, FL 33331, USA
Telephone: (954) 659-6020
Telefax: (954) 659-6021
Website: http://www.clevelandclinic.org/florida/research/cme
Which patient does not need preoperative radiation?

M. Büchler
Abteilung für Allgemeine, Viszerale und Transplantationschirurgie, Universitätsklinikum Heidelberg, Germany

The introduction of the concept of total mesorectal excision (TME) has changed the oncological outcome for the patients with rectal cancer, significantly. Since, all aspects of multimodal treatment have been challenged. Randomized controlled trials have shown that neoadjuvant treatment is superior to adjuvant treatment, which has been already implemented in the S3-guidelines. According to these guidelines all patients with locally advanced tumors (UICC stage II or III) should receive either neoadjuvant short term radiotherapy or neoadjuvant combined radiochemotherapy. In various trials was shown, that neoadjuvant treatment could significantly reduce the local recurrence rate. However, all treatment modalities, tested in randomized trials so far, could not show a survival benefit for the irradiated patients. On the other hand, neoadjuvant treatment caused acute and chronic toxicity and resulted in deteriorated anorectal, urinary and sexual function. Furthermore, radiation was associated with increased rates of malignant tumors, independent of the primary tumor. Therefore, strategies have to be developed, to identify patients at higher risk for locally recurrent cancer and to redefine the indications for neoadjuvant treatment. The available data indicates, that patients with tumors of the upper third of the rectum do not benefit from neoadjuvant treatment. The same seems to be true for patients with tumor infiltration of the mesorectum of less than 5 mm, no vascular invasion and a clear circumferential resection margin. These tumors seem to harbour a lower risk for local recurrence. The most promising indicator, however, seems to be the CRM itself. Various reports showed excellent oncological results without radiation, when the CRM was clear (> 1–2 mm) and a good quality TME was performed. Therefore, randomized controlled trials are overdue to question the neoadjuvant treatment in patients with no threatening of the mesorectal fascia (CRM > 2 mm), given, that an appropriate surgical TME can be offered.
Quality assurance in rectal cancer treatment

C.J.H. van de Velde, M.D., Ph.D.
President Elect ECCO, Department of Surgery, Leiden University Medical Center, Leiden, The Netherlands

Colorectal cancer is the cancer with the second highest cancer incidence in Europe. Roughly, one out of three patients with a colorectal malignancy has a rectal carcinoma. Surgery is the cornerstone in the curative treatment of rectal cancer. In the 1980s with conventional surgery, the 5-year local recurrence rate was over 20% and the 5-year overall survival rate around 50%. In the Swedish Rectal Cancer trial in which 1168 patients were included, preoperative radiotherapy in addition to conventional surgery resulted in a reduction of more than 50% in the 5-year local recurrence rate in comparison to conventional surgery alone (11% vs. 27%; p < 0.001). Besides, the 5-year overall survival rate improved from 48% to 58% if patients were treated with preoperative radiotherapy in addition to conventional surgery (p = 0.004). With the total mesorectal excision (TME), by which the rectum with its mesorectum and visceral fascia are dissected sharply and under direct vision, local recurrence rates dropped and overall survival improved. In the Dutch TME trial, 5 x 5 Gy preoperative radiotherapy in combination with TME surgery was compared to TME surgery alone (1861 patients). In this trial, the 5-year local recurrence rate for patients treated with TME surgery alone was similar to patients treated in the Swedish Rectal Cancer trial with blunt dissection in combination with preoperative 5 x 5 Gy radiotherapy (11%). If preoperative radiotherapy was added to TME surgery, 5-year local recurrence rate was reduced to 5.6%. The overall survival rate at 5 year was 64% for both patients treated with TME surgery alone and patients treated with preoperative radiotherapy followed by TME surgery, compared to 48% for patients treated with blunt dissection alone in the previously mentioned Swedish trial. TME surgery is now considered the standard surgical procedure for rectal cancer. However, even if TME surgery is performed, surgical quality varies. First, these results indicate that improvements in the surgical procedure itself can result in major progress regarding long-term oncological outcome such as decreased local recurrence rates and improved overall survival. Second, it illustrates that variation in surgical quality could lead to large differences in outcome. Recently, it was shown that surgical variation is not only important for patients with rectal cancer, but also plays an important role for the outcome of patients with colon cancer.
Session IX

Management of patients with stage IV colorectal cancer
Synchronous resectable colorectal liver metastases

Bernard Nordlinger, M.D., Antoine Brouquet, M.D.
Department of Digestive Surgery, Hôpital Ambroise Paré, Boulogne, France

Nearly 25% of patients with colorectal cancer present with liver metastases at the time of diagnosis. Only a minority of patients with synchronous colorectal liver metastases have resectable primary and metastatic disease. In patients with resectable synchronous disease, despite complete resection of all tumor deposits cancer relapse can occur in nearly 70% of cases. The treatment strategy in patients with synchronous resectable liver metastases with primary tumor in place depends on several factors including the site of the primary tumor, associated symptoms, intestinal obstruction in particular, the need for pre-operative radiation or chemoradiation in patients with rectal primary, the extent of metastatic disease, and response to chemotherapy of both primary tumor and liver metastases. Given the severity of this disease and the high risk of progression even after complete resection, our policy is to try to control metastatic disease first with systemic chemotherapy in the absence of complications related to the primary tumor before considering surgery.

Simultaneous resections can be safely performed after short course chemotherapy in patients with colon or rectal cancer and liver metastases with limited extent. Resection of primary tumor with or without preoperative chemoradiation is preferred in patients at risk of primary related complications. A reverse approach (liver resection first before resection of primary tumor) is useful in patients with advanced metastatic disease requiring major liver resection in particular in patients with rectal primary. In this latter setting, chemoradiation can be administered using conventional of hypofractionned protocol after resection of liver metastases. Multiplicity and complexity of treatment strategies to synchronous colorectal cancer and liver metastases underline the need for a multidisciplinary approach to this disease.
Surgical results after downstaging of initially marginal or non-resectable liver metastases

Jacques Belghiti
HPB Surgery, Beaujon Hospital, 92110 Clichy, France – University Paris 7 Denis Diderot

It is generally admitted that only liver resection can achieve curative treatment for resectable patients with CRLM. In patients initially considered unresectable, both refinements in surgical technique using portal vein occlusion or two step resections and increased efficiency of chemotherapy regimen with the adjunction of antiangiogenics now allow secondarily resection. Recent evidences suggest almost identical long term survivals in case of secondarily downstaged lesions advocating an aggressive approach. However, these data lie on disparate and non consensual criteria for unresectability which often don’t take into account technical and carcinological components together. Furthermore, both impaired general status and damaged underlying parenchyma as a consequence of prolonged chemotherapy to achieve resectability as well as the technical challenge required to perform adequate carcinologic resection could increase the operative risk in such patients. Downstaged CRLM initially unresectable was defined technically by a major resection after volumetric modulation (portal vein occlusion required) and oncological criteria (≥ 12 cycles or change of chemotherapy regimen to achieve sufficient response). In our experience this subgroup experienced both high morbidity and mortality. Complicated postoperative course jeopardizes postoperative chemotherapy and could subsequently put some patients at increased risk of recurrence. Whether all these patients preoperatively controlled by chemotherapy actually benefit such an aggressive approach is a matter of ongoing debate which therefore needs a reappraisal.
Stage IV colorectal cancer. Hyperthermic intraperitoneal chemoperfusion (HIPEC) in peritoneal carcinomatosis

Ramon Salazar, Pedro Barrios
Catalan Institute of Oncology, Hospital Duran i Reynalds, Hospital Moisès Broggi, Peritoneal Carcinomatosis and HIPEC Program of the Catalan Oncological Plan, Barcelona, Spain

Peritoneal carcinomatosis (CP) is observed in 10–20% of stage IV colorectal cancer patients and confers poor prognosis in some cases, particularly when other sites are also affected (Kohne, Cunningham et al. 2002; Van Cutsem, Kohne et al. 2009). It is similar to liver mets in that a regional pathway of dissemination is plausible (Elias 2004). Therefore a similar regional approach can be conceptually pursued. Currently, liver surgery for liver mets is universally accepted despite the lack of randomized trials, as long as the disease is found amenable to radical resection (Abad, Figueras et al. 2007).

In published reports, peritoneal debulking surgery plus HIPEC (complex treatment) yield median survival times of 12–34 months. Only one phase III trial has been finalized (Verwaal et al.), in which complex treatment plus subsequent palliative chemotherapy almost doubled the median survival time achieved with palliative chemotherapy alone (22.3 m vs. 12.6 m). Another randomized trial was closed early due to insufficient recruitment (Mahteme, Hansson et al. 2004) and 2 other non randomized comparative studies (Mahteme, Hansson et al. 2004; Elias, Lefevre et al. 2009) and a systemic revision (Cao, Yan et al. 2009) support the use of complex treatment. This has been reflected in national and international guidelines, including those of the prestigious NICE.

In order to select the right patient candidates for complex treatment a number of prognostic indexes have been published Lyon Index, Peritoneal Cancer Index (PCI Sugarbaker), Simplified Peritoneal Cancer Index (Netherlands Institute), most of which are based in the anatomical extension and distribution of the implants (Elias, Gilly et al.; Glehen, Kwiatkowski et al. 2004; Harmon and Sugarbaker 2005; Sugarbaker 2005; Sugarbaker 2005; Gilly, Cotte et al. 2006; Yan, Black et al. 2006). All these are intraoperative or at best, can be sought at laparoscopy. Histopathological data can help in appendiceal primaries or pseudomixoma (Bruin, Verwaal et al.; Glehen, Mohamed et al. 2004; Mahteme and Sugarbaker 2004; Sugarbaker 2005), and more recently, also in CRC (Bruin, Verwaal et al.).

We, at the Catalan Institute of Oncology, along with the HIPEC Catalan Program led by Dr Barrios are in the process of validating both clinical (pre-operative) and operative-pathological prognostic index, with the objective to further refine which patient will derive the greatest benefit from debulking intraoperative surgery and HIPEC and which patients are not good candidates for such a complex treatment strategy. In the meantime we favor the indication in fit patients with a PCI less than 21 and no signs of unresectability.
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List of Chairpersons, Speakers and Scientific Organizers

PD Dr. Mario Anders
Interdisziplinäre Endoskopie
Universitätsklinikum Eppendorf
Martinistr. 52
20251 Hamburg
Germany

Dr. Badma Bashankaev
National Research Center of Surgery
Department of Colorectal and Pelvic Floor Surgery
2 Abrikosovsky per.
119992 Moskau
Russia

Dr. Jacques Belghiti
Hôpital Beaujon
Department of Surgery
100, Bd. Général Leclerc
92118 Clichy
France

PD Dr. Andreas Bembenek
Chirurgie
Klinikum Region Hannover
Klinikum Siloah
Roesebeckstr. 15
30449 Hannover
Germany

Mariana Berho, M.D.
Professor of Medicine
Cleveland Clinic Florida
Department of Pathology
2950 Cleveland Clinic Boulevard
Weston, FL 33331
USA

Prof. Dr. Dr. h.c. mult.
Markus Büchler
Allgemein-/Viszeralchirurgie
Universitätsklinikum Heidelberg
Im Neuenheimer Feld 110
69120 Heidelberg
Germany

Prof. Dr. Heinz J. Buhr
Allgem.,Gefäß- u.Thoraxchirurgie
Charité – Universitätsmedizin
Campus Benjamin Franklin (CBF)
Hindenburgdamm 30
12203 Berlin
Germany

Prof. Sir John Burn
Institute of Genetic Medicine
Newcastle University
Central Parkway
Newcastle upon Tyne NE13BZ
Great Britain

Prof. Dr. Dr. h.c. mult.
Meinhard Classen
Golfweg 11
6370 Reith b. Kitzbühel
Austria

Prof. Dr. Pierre-Alain Clavien
Universitätsspital Zürich
Visceralchirurgie
Rämistr. 100
8091 Zürich
Switzerland

PD Dr. Stefan von Delius
Innere Medizin II
Klinikum rechts der Isar
der Technischen Universität
Ismaninger Str. 22
81675 München
Germany

Prof. Dr. André D'Hoore
University Ziekenhuis
Gasthuisberg
Dept. Abdominal Surgery
Hereestraat 49
3000 Leuven
Belgium
Prof. Dr. Michael Fried
Universitätsspital Zürich
Gastroenterologie/Hepatologie
Rämistr. 100
8091 Zürich
Switzerland

Prof. Dr. Helmut Friess
Chirurgie
Klinikum rechts der Isar
der Technischen Universität
Ismaninger Str. 22
81675 München
Germany

Prof. Dr. Christoph-Thomas Germer
Chirurgie I
Klinikum der
Universität Würzburg
Oberdürrbacher Str. 6
97080 Würzburg
Germany

Prof. Dr. Michael Ghadimi
Allgemein-Chirurgie
Universitätskliniken Göttingen
Robert-Koch-Str. 40
37075 Göttingen
Germany

Prof. Dr. Burkhard Göke
Medizinische Klinik II
Klinikum der Universität
München – Großhadern
Marchioninistr. 15
81377 München
Germany

Prof. Dr. Florian R. Greten
Innere Medizin II
Klinikum rechts der Isar
der Technischen Universität
Ismaninger Str. 22
81675 München
Germany

Prof. Dr. Dieter Hahnloser
BH10/983
C.H.U.V.
Service de Chirurgie Viscérale
Rue du Bugnon 46
1011 Lausanne
Switzerland

Curtis C. Harris, M.D.
Professor of Medicine
National Cancer Institute
Center for Cancer Research
Laboratory of Human Carcinogenes
31 Center Drive
Bethesda, MD 20892
USA

Hans Herfarth, M.D.
Associate Professor of Medicine
University of North Carolina
Gastroenterology & Hepatology
4151 Bioinformatics Bldg.
130 Mason Farm Road
Chapel Hill, NC 27599-7080
USA

Prof. Dr. Heinz Höfler
Allgemeine Pathologie/Anatomie
Klinikum rechts der Isar
der Technischen Universität
Ismaninger Str. 22
81675 München
Germany

Prof. Dr. Dr. h.c. Werner Hohenberger
Chirurgische Klinik und Poliklinik
Universitätsklinikum Erlangen
Krankenhausstr. 12
91054 Erlangen
Germany

Prof. Dr. Drbjorn Holm
Karolinska University
Hospital Solna
Institution for Molecular Medicine & Surgery
171 76 Stockholm
Sweden
Thomas F. Imperiale, M.D.
Professor of Medicine
Indiana University
School of Medicine
Division of Gastroenterology
1050 Wishard Blvd.
Indianapolis, IN 46202
USA

PD Dr. Klaus-Peter Janssen
Chirurgie
Klinikum rechts der Isar
der Technischen Universität
Ismaninger Str. 22
81675 München
Germany

Dr. Gabriella Jansson-Palmer
Karolinska University Hospital Solna
Department of Molecular Medicine & Surgery
171 76 Stockholm
Sweden

Prof. Dr. Karl-Walter Jauch
Chirurgie
Klinikum der Universität
München – Großhadern
Marchioninistr. 15
81377 München
Germany

Prof. Dr. Michael Jung
Innere Medizin
Katholisches Klinikum Mainz
St. Hildegardis-Krankenhaus
Hildegardstr. 2
55131 Mainz
Germany

Prof. Dr. Daniela Kandioler
Medizinische Universität Wien
Klinik für Chirurgie
Leitstelle 21A
Währinger Gürtel 18–20
1090 Wien
Austria

Prof. Dr. Alex Kartheuser
Clinique St. Luc
Service de Chirurgie
de l'Appareil Digestif
Avenue Hippocrate 10
1200 Bruxelles
Belgium

Prof. Dr. David J. Kerr
University of Oxford
Department of Clinical Pharmacology
Old Road Campus off Roosevelt Dr
Oxford OX3 7DQ
Great Britain

Prof. Dr. Thomas Kirchner
Pathologie
LMU München
Thalkirchner Str. 36
80337 München
Germany

Prof. Dr. Christoph A. Klein
Pathologie
Universitätsklinikum Regensburg
93042 Regensburg
Germany

Prof. Dr. Martin E. Kreis
Chirurgie
Klinikum der Universität
München – Großhadern
Marchioninistr. 15
81377 München
Germany

David Alan Lieberman, M.D.
Professor of Medicine
Oregon Health & Science Univ.
Division of Gastroenterology
L461
3181 SW Sam Jackson Park Road
Portland, OR 97239
USA
Prof. Dr. Karl-H. Link
Chirurgie
Aklepios Paulinen Klinik
Geisenheimer Str. 10
65197 Wiesbaden
Germany

Prof. Dr. Christoph A. Maurer
Kantonsspital
Chirurgische Klinik
Rheinstr. 26
4410 Liestal
Switzerland

Prof. Dr. Alexander Meining
Innere Medizin II
Klinikum rechts der Isar
der Technischen Universität
Ismaninger Str. 22
81675 München
Germany

Prof. Dr. Michael Molls
Strahlentherapie
Klinikum rechts der Isar
der Technischen Universität
Ismaninger Str. 22
81675 München
Germany

Prof. Dr. Horst Neuhaus
Innere Medizin
Evangelisches Krankenhaus
Kirchfeldstr. 40
40217 Düsseldorf
Germany

Prof. Dr. Markus F. Neurath
Medizinische Klinik 1
Universitätsklinikum Erlangen
Ulmweg 18
91054 Erlangen
Germany

Prof. Dr. Aviram Nissan
Division of Surgical Oncology
Rabin Medical Center
Beilinson Campus
Department of Surgery B
P.O. Box 9064
49190 Petah Tiqva
Israel

Prof. Dr. Bernard Nordlinger
Hôpital Ambroise Paré
Department of Digestive Surgery
92104 Boulogne
France

Prof. Dr. P. Ronan O'Connell
St. Vincent's Hospital
Department of Surgery
Elm Park
Dublin 4
Ireland

Philip B. Paty, M.D.
Memorial Sloan-Kettering
Cancer Center
Department of Surgery
Colorectal Service
1275 York Avenue
New York, NY 10065
USA

Prof. Dr. Aurel Perren
Universität Bern
Pathologisches Institut
Murtenstr. 31
3010 Bern
Switzerland

Prof. Dr. Phil Quirke
St. James’s University Hospital
Pathology and Tumour Biology
Wellcome Trust Brenner Bldg.
Beckett Street
Leeds LS9 7TF
Great Britain
Prof. Dr. Eric van Cutsem
University Ziekenhuis
Gasthuisberg
Gastro-entérologie
Herestraat 49
3000 Leuven
Belgium

Prof. Dr. Cornelis J.H. van de Velde
Academisch Ziekenhuis Leiden
Department of Surgery
Albinusdreef 2
2333 ZA Leiden
The Netherlands

PD Dr. Carsten T. Viehl
Universitätsspital Basel
Viszeralchirurgie
Spitalgasse 21
4031 Basel
Switzerland

Dr. Klaus Weber
Chirurgische Klinik und Poliklinik
Universitätsklinikum Erlangen
Krankenhausstr. 12
91054 Erlangen
Germany

Steven D. Wexner, M.D.
Professor of Medicine
Cleveland Clinic Florida
Department of Colorectal Surgery
2950 Cleveland Clinic Boulevard
Weston, FL 33331
USA
POSTER ABSTRACTS

Poster Numbers 1 – 79

Author Index to Poster Abstracts
The sphincter’s fate in low lying rectum cancer: A decision analysis

M. Adamina, S. Wolf, B. Hummel, F. Näf, S. Bischofberger, T. Steffen
Klinik für Chirurgie, Kantonsspital St. Gallen, St. Gallen, Switzerland

Introduction: Abdominoperineal resection (APR) is indicated for rectal cancers located within 5 cm from the anal verge. Intersphincteric resection (ISR) is an alternative procedure preserving the anal sphincter and avoiding a permanent colostomy. Concerns about a less radical procedure causing worse oncological results and poor continence have precluded the widespread use of ISR. A decision analysis was performed to investigate the relative benefits and harms of ISR and APR.

Methods: A Markov model including 18 different health states was built using data from the Swedish Rectal Cancer Registry and a systematic review of the literature on ISR. Outcome measures compared the quality adjusted life expectancy and crude survival rates of patients undergoing APR or ISR.

Results: For a stage II rectal cancer, ISR was the preferred strategy with a gain of 1.35 quality-adjusted life years (QALY) over APR (ISR 8.90 QALY vs. APR 7.55 QALY). This result was not caused by a difference in crude survival: both strategies displayed similar 5-year mortality rates (ISR 70.1% vs. APR 69.4%). It was, however, influenced by surgical mortality and by the development of metastases. On the other hand, the occurrence of fecal incontinence had marginal influence on the preference of patients for ISR. Overall, the disutility of a colostomy drove the preference for ISR through the model. Preference for ISR was conserved across stage I, stage II, and stage III rectal cancers.

Discussion/Conclusion: From a patient’s point of view, ISR is the preferred strategy for resection of a low lying rectal cancer, notwithstanding an imperfect continence.
Results of intraoperative pelvic hyperthermic chemotherapy for treatment of locally advanced rectal carcinoma

M. Alekseev, E. Rybakov
State Research Center of Coloproctology, Moscow, Russia

Objectives: The standard treatment for stage T3–T4 rectal carcinoma is neoadjuvant chemoradiation (CRT) + surgery. Complicated tumor, poor general condition of patient or refusal of radiation are obstacles for CRT. Intraoperative pelvic hyperthermic chemotherapy (IOPHC) is a possible alternative for resectable locally advanced T3–T4 mid- and low rectal carcinoma in patients not suitable for CRT.

Methods: IOPHC performed after removal of tumor using solution containing 150 mg of cisplatin in 1000 ml of saline, at 45.0°C during 60 min in pelvic cavity.

Results: Sixty consecutive patients were undergone IOPHC. Sixty patients treated by surgery only were selected as retrospective control. All patients had locally advanced T3–T4 mid- and low rectal carcinomas. Groups were well matched in terms of tumor histology (in IOPHC group G1–2 was 44/60 (73%), in retrospective – 43/60 (72%) and primary invasion (in main group T3 was 51/60 (85%), in retrospective – 47/60 (78%), except lymph node status (N1–2 – 31/60 (52%) vs. 27/60 (45%) patients, consequently). There was no difference in type of operation between groups. In 30% of cases resection of adjacent organs was necessary. There was no evidence of IOPHC related toxicity. Surgically morbidity was 15/60 (25%) vs. 17/60 (28%), respectively (p = 1.0). At median follow-up of 38 months local recurrences developed in 5 (8.3%) patients of IOPHC group and in 9 patients (15%) of control group (p = 0.2). IOPHC didn’t result reduction of distant metastases rate, i.e. distant recurrence developed in 8/60 (13%) patients in each group. 3-year DFS was 75% in IOPHC vs. 63% – in control, 4- and 5-year DFS was 72% vs. 63% (p = 0.36), consequently.

Conclusion: Despite non-randomized character of the study 2-fold decrease of local recurrence rate of advanced rectal carcinoma has been found. IOPHC is well tolerated procedure for frail patients with contraindication to CRT.
Extranodal non-Hodgkin's lymphomas of gastrointestinal tract

Daniela Badea, M. Badea, Amelia Genunche
UMF Craiova, Dolj, Romania

Introduction: The gastrointestinal tract (GI) is the predominant site of extranodal non-Hodgkin's lymphomas (NHLs). Primary NHLs of the GI tract are rare, accounting for only 1 to 4% of malignancies with this localisation.

Methods: During the last 15 years there were registered 19 patients with primary GI NHLs.

Results: The stomach is the most frequently affected part of the GI 73.68%, being followed by the colonic 21.05% and intestinal localization 10.55%. Histologic 68.42% are extranodal marginal zone B-cell lymphoma of MALT type (E-MZL), 21.05% diffuse large-B cell lymphoma (DLCL), and 10.55% mantle cell lymphoma (MCL). Gross pathology of these tumors differs: a mass or polypoid lesion with or without ulceration in 63.15%, benign-appearing gastric ulcer in 42.1%, nodularity thickened, cerebroid gastric folds in 21.5% of cases and infiltrative lesions in 16%. The majority of lesions are unifocal but 10.55 are multiple extralymphoid determinations. The medium age of the lot is 58 ± 4 years and the sex ratio favor male gender 63.15%. 8 (42.1%) cases are localized stage (IE/IIE) and 87.5% of this are E-MZ, while only 63.63% of the advanced stages are of E-MZL type. No matter which is the histology and localization primarily symptom was the abdominal pain present in 89.47% of the cases, followed by anorexia in 50% of the cases and weight loss in 30% of the cases. The evolution of symptoms from the debut to the diagnostic ranges from 4 weeks to one year.

Discussion/Conclusion: Despite their rarity, primary NHL lymphomas of the GI tract are important, since their management and prognosis are distinct from that of adenocarcinomas of the GI tract.
Incidence and clinical evolution of non-Hodgkin lymphoma (NHL) of the colon

M. Badea, Daniela Badea, Amelia Genunche, Laura Stefan, A. Badea, Doriana Duta
UMF Craiova, Dolj, Romania

Introduction: The gastrointestinal (GI) tract is the predominant site of extranodal non-Hodgkin lymphomas (NHLs). Primary NHLs of the GI tract is rare, but the secondary GI involvement is relatively common.

Methods: Our study aims to assess the incidence of primary and secondary involvement of the colon in the NHL. Endoscopic evaluation is an ideal way for verifying the extension and also for the collection of biopsy material.

Results: Between 2000–2009 our department has collected 756 NHL (except: CLL, hairy cell leukemia and mycosis fungoides). Of the 17 NHL (2.24%) with primary gastrointestinal lymphoma 14 (82.35%) had gastric involvement and only 2 (0.26% from all lymphomas) had colorectal lesions, one of the cases presented multiple lesions (gastric and colonic). Immunohistology was concordant with MALT. Endoscopic appearance was nodular lesions ulcerated in one case and infiltrative in other.

At diagnosis, secondary lymphoma involvement to the digestive tract were seen in 68 (8.99%) of patients, with only 11 with colon lesions (1.45% for all lymphoma and 16.17% from all gastrointestinal secondary lymphoma involvement). Histological, three cases were Burkitt-like, four mantle cell lymphoma, two large cell lymphoma, three follicular lymphoma. Four cases had active HIV infection (three, Burkitt and 1 large cell lymphoma).

Endoscopic appearance was nodular and nodular ulcerative lesions in 8 cases, the other 3 cases were infiltrative appearance, two of them presenting also ulcerative lesions.

Colorectal lymphoma may present with abdominal pain 5 (45.45%), overt or occult bleeding 5 (45.45%), diarrhea 3 (27.27) or rarely, bowel obstruction (9%).

Discussion/Conclusion: Our study confirms the rarity of primary involvement of colon by lymphoma lesions. Secondary colonic lesions are more common, predominant histology were Burkitt-like/large cell (HIV+) and mantle cell lymphoma.
The Ann Arbor Staging system versus modified Blackledge Staging system and Musoff system in the gastrointestinal lymphoma

M. Badea, Daniela Badea, Amelia Genunche, Cristina Petrica, Doina Iordache, Laura Stefan, Doriana Dutu, A. Badea
UMF Craiova, Dolj, Romania

Introduction: The gastrointestinal tract is the most commonly involved extranodal site for non-Hodgkin lymphoma (NHL), accounting for up to half of all extranodal cases. Primary GI lymphomas can be operationally defined as lymphomas in which the main bulk of disease is confined to the GI tract, necessitating treatment directed toward that site.

Methods: During the last 10 years, there were registered 24 lymphoma lesions with gastric determinations. Staging procedures for gastric lymphoma include history physical examination, imagistic technique for thorax and abdomen, hematological, renal and liver evaluations, laboratory tests, LDH, b2-microglobulin levels, gastroduodenal endoscopy with multiple gastric biopsies, and recently gastric ultrasound endoscopy (EUS).

Results: From the 24 cases with gastric lymphoma, ten (47.61%) was high-grade four 40% of this with a low-grade component, 11 (45.83%) low-grade MALT lymphoma, 2 (8.33%) follicular lymphoma and 1 (4.16%) mantle zone lymphoma. The Ann Arbor Staging system is used but it is compared with the GI-lymphoma-specific Blackledge, Musoff or Ann Arbor revised system. EUS may facilitate the accurate estimation of both the depth of invasion and involvement of regional lymph nodes. It is superior to CT scan in false negative cases, but CT evaluates the non-contiguous subdiaphragmatic lymph nodes. The stadial distributions of our lot with MALT lymphoma is: IE 63%, II<sub>E</sub> 17%, II<sub>E</sub>Ei 7%, III 2%, IV 10% and for the rest of lymphoma histological subtype IE 27%, II<sub>E</sub>Ei 24%, II<sub>E</sub>EII 17%, IIIE 8.5%, IVE 24%.

Discussion/Conclusion: The type of staging system has no evident impact in our study, but several authors have suggested that such staging modification may be of prognostic significance.
Capnography improves patient safety during propofol sedation for colonoscopy: A randomized, controlled study (ColoCap Study)

Analena Beitz¹, Andrea Riphaus²,a, Alexander Meining¹, Tim Kronshage², Christoph Geist², Stefan Wagenpfeil³, Andreas Weber¹, Andreas Jung¹, Monther Bajbouj¹, Christian Pox², Gerhard Schneider⁴, Roland M. Schmid¹, Till Wehmann⁵, Stefan von Delius¹

II. Medizinische Klinik und Poliklinik¹ and Institut für Medizinische Statistik und Epidemiologie³, Klinikum rechts der Isar, Technische Universität München, Medizinische Universitätsklinik², Knappschaftskrankenhaus, Ruhr-Universität Bochum, Zentrum für Anästhesie, Notfallmedizin und Schmerztherapie⁴, Helios Klinikum Wuppertal and Fachbereich Gastroenterologie⁵, Deutsche Klinik für Diagnostik, Wiesbaden, Germany

aBoth authors contributed equally to this study.

Introduction: Capnography provides a non-invasive monitoring of ventilation and could help to prevent respiratory adverse events during procedural sedation. The aim of this randomized study was to determine whether intervention based on additional capnographic monitoring reduces the incidence of arterial oxygen desaturation during propofol sedation for colonoscopy.

Methods: Patients (ASA 1–3) scheduled for colonoscopy under propofol sedation were randomly assigned to either a control arm with standard monitoring (pulse oximetry, automated blood pressure readings and ECG in patients with cardiac disease; standard arm) or an interventional arm in which additional capnographic monitoring (Capnostream 20, Oridion, US; capnography arm) was available. All patients routinely received 2 l/min of supplemental oxygen. In both study arms detection of apnea or altered respiration induced withholding propofol administration, stimulation of the patient, chin lift maneuver or further measures. The primary study end point was the incidence of arterial oxygen desaturation (defined as a fall in oxygen saturation of ≥ 5% or < 90%); secondary end points included the occurrences of hypoxemia (SpO₂ < 90%), severe hypoxemia (SpO₂ ≤ 85%), bradycardia, hypotension and the quality of sedation (patient cooperation and patient satisfaction).

Results: 760 patients were enrolled at three German endoscopy centers. The per-protocol analysis revealed a significant reduction of the incidence of oxygen desaturation in the capnography arm in comparison to the standard arm (41.3% vs. 55.1%; P < 0.001). The numbers of patients with a fall in oxygen saturation < 90% and ≤ 85% were also significantly different (12.6% vs. 21.7%; P = 0.002 and 3.6% vs. 7.8%; P = 0.020). There were no differences regarding the rates of bradycardia and hypotension. Quality of sedation was similar in both groups. Results of statistical analyses were maintained for the intention-to-treat population.

Discussion/Conclusion: Additional capnographic monitoring of ventilatory activity reduces the incidence of oxygen desaturation and improves safety of propofol sedation for colonoscopy.
Are there other indicators of quality of colonoscopy than adenoma detection rate (ADR)?

Marek Benes, Pavel Drastich, Tomas Hucl, Petr Stirand, Pavel Wohl, Julius Spicak
IKEM, Department of Gastroenterology and Hepatology, Prague, Czech Republic

Introduction: Caecum intubation rate (CR) is historically the most commonly used indicator of quality of colonoscopy. However, nowadays this indicator is not enough and it has been frequently replaced by adenoma detection rate (ADR) in combination with extraction time (ET). The aim of our study was to evaluate various parameters of colonoscopy in order to develop a new more precise indicator of quality of colonoscopy.

Method: We have used a structured database used to generate medical reports about colonoscopies at our endoscopy unit for retrospective evaluation. This database is interconnected with a register of histological findings which provided data about histological examinations. The individual data was statistically evaluated using correlation tests (Spearman’s coefficient).

Results: We have evaluated 1360 consecutive colonoscopies altogether, which were carried out by 6 experts. Each one of the endoscopists had performed more than 250 colonoscopies in a year and more than 1000 colonoscopies during his carrier. The average time of the procedure was 16 minutes (10–23 min.). CR was 96% (93–97%), reaching of terminal ileum 90% (87–93%), ADR 30% (21–40%), the average number of polyps in colonoscopies where polyps were found was 2.4 (2.1–2.7), detection of colorectal cancer 4% (3–5%), detection of flat lesions 8% (5–11%). Correspondence of histological findings with evaluation of polyps using KUDO classification was 91% (86–96%). The percentage of extracted significant polyps was 80% (66–93%). The histologically complete polypectomy rate (HCPR) of significant polyps was 51% (32–69%). The percentage of colonoscopies without pre-medication was 44% (30–58%). The time between polypectomy of significant lesion and check up colonoscopy was 15 months (6–24). The percentage of complications after therapeutic colonoscopies was 1% (0–2%).

Conclusion: ADR is above 20% which is a tolerable lower limit. ADR of the individual experts appears to be a factor which is not dependent on the length of the procedure and on the CR. The HCPR significantly correlates with the ADR, the length of procedure and CR. The HCPR appears to be an ideal indicator of the quality of a colonoscopy.
Quality of endoscopic mucosal resection (EMR) at IKEM

M. Beneš, P. Drastich, P. Štirand, P. Wohl, T. Hucl, J. Špičák
IKEM, Prague, Czech Republic

Introduction: Endoscopic mucosal resection (EMR) together with endoscopic submucosal dissection (ESD) have become standard methods of treatment of gastrointestinal tract (GIT) neoplasia in cases with clear indications. The long term results of these methods depend not only on strict adherence to indication criteria but in particular on the precision of the procedure. The goal of our study was to evaluate histological completeness of EMR and the extent of recurrence of neoplasia after EMR.

Method: We have retrospectively analyzed a structured database of medical reports of colonoscopies at our endoscopy unit. This database is interconnected with a register of histological findings. The data were statistically evaluated using correlation tests (Spearman’s coefficient).

Results: We have evaluated 5282 consecutive colonoscopies altogether, which were carried out by 6 experts. Each one of the endoscopists had performed more than 250 colonoscopies/year and more than 1000 colonoscopies during his carrier. The average time of colonoscopy was 16 minutes (10–23 min.). Caecum intubation rate (CR) was 96% (93–97%), reaching of terminal ileum 90% (87–93%), Adenoma detection rate (ADR) 30% (21–40%), detection of colorectal cancer 4% (3–5%), detection of flat lesions 8% (5–11%). Correspondence of histological findings with evaluation of polyps using KUDO classification was 91% (86–96%). In total 352 EMR were carried out in 316 patients. The percentage of histologically complete EMR (complete removal of lesion with histologically proven margin free of neoplasia) of significant polyps and flat lesions was 42% (21–63%). The recurrence of neoplasia after EMR occurred in 73 patients (20%) and in 15 of them (4%) further endoscopic removal was not possible. The average interval between EMR and control colonoscopy was 5 months (2–8 M). The percentage of complications after EMR was 2% (1–3%).

Conclusion: EMR is a safe and effective therapy of advanced neoplasia in GIT. The proportion of histologically complete EMR was low with a corresponding high neoplasia recurrence rate. The most likely reason may be the high popularity of piece-meal EMR instead of more precise en-block EMR or ESD.
Compartmental differences of circulating tumor cells in colorectal cancer

Ulrich Bork, Nuh N. Rahbari, Alexandra Kircher, Eva Seyfarth, Thomas Niemetz, Sebastian Schölch, Christoph Kahlert, Markus W. Büchler, Moritz Koch, Jürgen Weitz
Department of General, Visceral and Transplantat Surgery, University of Heidelberg, Im Neuenheimer Feld 110, 69120 Heidelberg, Germany

Introduction: The prognostic role of circulating tumor cells (CTC) has been established for colorectal cancer (CRC). We investigated the qualitative and quantitative detection of CTC in the central (CVBC) and mesenteric venous blood compartments (MVBC) to elucidate the patterns of hematogenous tumor cell dissemination in patients with CRC.

Methods: A total of 200 patients were enrolled prospectively. Blood samples were collected from the tumor-draining vein and via a central venous line. CTC were detected and quantified using the CellSearch System. Factors associated with CTC detection in both compartments were analyzed using univariate and multivariate analyses.

Results: CTC analyses were performed in the CVBC and MVBC in 200 and 80 patients, respectively. CTC were found at a higher rate (p = 0.01) and at a higher count (p = 0.006) in the MVBC compared to the CVBC. On multivariate analyses stage IV disease (Odds ratio = 3.83; 95% confidence interval 1.42–10.35) and elevated preoperative CA 19-9 level (3.57; 1.30–9.79) were associated with CTC detection in the CVBC. CTC were detected more frequently (p = 0.05) and at higher numbers (p = 0.05) in the CVBC of patients with low compared to mid/high rectal tumors.

Discussion/Conclusion: The qualitative and quantitative detection of CTC is higher in the MVBC compared to the CVBC of patients with CRC. These data support the cascade theory of tumor cell dissemination in CRC.
Non-invasive screening for colorectal cancer and colon adenomas

S. Chernyshov¹, E. Zenkina²
¹State Research Center of Coloproctology, Moscow, Russia
²Moscow P.A. Herzen Research Oncological Institute, Russia

Aim: to evaluate the diagnostic sensitivity of quantitative ELISA tests for detection of human hemoglobin (hHb), human hemoglobin-haptoglobin complex (hHb/Hp) and fecal pyruvate kinase-M2 (tumor M2-PK) in feces of patients with colorectal cancer (CRC) and colon adenomas.

Methods: Stool samples were obtained from 95 patients with confirmed CRC, 17 patients with colon adenomas and 48 healthy individuals without any lesions in colon or anus by data of colonoscopy. The content of hHb, hHb/Hp and tumor M2-PK was investigated.

Results: hHb had the highest sensitivity concerning CRC 84/95 (88.4%), while tumor M2-PK and hHb/Hp were elevated in 75/95 (78.8%), and 72/95 (76.0%), consequently.
The presence of colon adenomas was associated with elevation of tumor M2-PK in 5/17 (29.4%) patients. hHb and hHb/Hp was elevated in 4/17 (23.5%) 2/17 (11.8%) cases consequently.
In healthy individuals elevation of levels of tumor M2-PK were identified in 7/48 (17.9%) cases. Human hemoglobin was elevated in 3/48 (6.3%) cases, while none of healthy individuals were diagnosed with hHb/Hp in stool.

Conclusion: The fecal ELISA test are sensitive in CRC and colon adenomas and can be used as non-invasive screening tool.
Is the prevalence of colorectal adenoma higher in patients with gastric neoplasm?

Chang Hwan Choi, Bong Ki Cha, In Do Song, Suh Yoon Yang, Se Kyung Chang
Department of Internal Medicine, Chung-Ang University College of Medicine, Seoul, South Korea

Introduction: Colorectal cancer is more frequently detected among primary gastric cancer patients. We aimed to compare the prevalence of colorectal adenomas between patients with gastric neoplasm and healthy controls.

Methods: This study was retrospectively performed in Chung-Ang University Hospital from January 2005 through June 2010. A total of 172 patients with gastric neoplasm who underwent colonoscopy were enrolled. Age and sex matched 860 subjects without gastric neoplasm who underwent colonoscopy in health promotion center were enrolled as the controls. Various factors were evaluated such as gender, age, body mass index (BMI), abdominal circumference, and the frequency of multiple (≥ 2 sites), large (≥ 1 cm) and proximal (cecum to splenic flexure) colorectal adenomas. Advanced colorectal adenoma was defined by any of the followings; (1) polyp size at least 1.0 cm, (2) containing > 25% villous features, or high-grade dysplasia, or adenocarcinoma by histologic examination.

Results: The sex ratio was 132:40 (male:female) in the gastric neoplasm group and 662:198 in the controls. The mean age was 59.6 ± 9.9 in the gastric neoplasm group and 57.9 ± 10.0 in the controls. BMI and abdominal circumference were greater in the controls than in the gastric neoplasm group (23.1 ± 2.9 vs. 24.2 ± 2.8 and 79.7 ± 2.9 vs. 83.7 ± 2.8, respectively). Among 172 patients with gastric neoplasm, low grade dysplasia, high grade dysplasia, and adenocarcinoma were 54, 5, and 113 patients, respectively. The prevalence of colorectal adenoma and multiple adenomas were tended to be higher in the gastric neoplasm group than in the controls (36.9% vs. 29.9%, and 17.7% vs. 12.2%, respectively, p > 0.05). The prevalence of advanced, large and proximal colon adenomas were significantly higher in the gastric neoplasm group than in the controls (11.5% vs. 3.0%, 10.8% vs. 4.5%, and 26.2% vs. 16.7%, respectively, p < 0.05). These results were similar with those in the subgroup analyses among subjects without general and abdominal obesity. In the regression analyses, the odds ratios of advanced, large and proximal colon adenomas were 4.5 (95% CI: 2.5–8.2), 2.3 (95% CI: 1.3–3.9), and 1.6 (95% CI: 1.1–2.3), respectively, in the patients with gastric neoplasm compared to the controls.

Discussion/Conclusion: The prevalence of advanced colorectal adenoma and proximal colon adenoma were significantly higher in patients with gastric neoplasm than in healthy subjects. The patients with gastric adenoma or adenocarcinoma may need more vigorous screening for colorectal adenoma.
Gradual loss of functional gap junction within progression from colorectal adenoma to cancer – A shift from membranous CX32 and CX43 expression to cytoplasmic pattern during colorectal carcinogenesis

Regina Dereniewicz-Wincewicz¹, Andrzej Wincewicz², Luiza Kanczuga-Koda³, Mariusz Koda⁴, Stanislaw Sulkowski⁴
¹Polyclinic of Ministry of Administration and Interior Affairs, Kielce, Poland
²Specialist Medical Practice – Pathologist Bialystok, Poland
³Department of Pathology, Maria Skłodowska-Curie Memorial Bialystok Oncology Center
⁴Department of General Pathomorphology, Medical University of Bialystok, Collegium Pathologicum, Bialystok, Poland

Introduction: Cell to cell signaling via GAP junctions is important in mediation of cell growth inhibition and counteracts uncontrolled cell proliferation. GAP junctions are composed of connexins (CX). The role of connexins have been investigated in carcinogenesis and cancer progression. The aim of this study was the assessment of expression and location of CX32 and CX43 in colorectal adenomas and carcinomas as well as analysis of expression of these proteins in association with clinical and pathological features of tumors and evaluation of mutual relationships between CX32 and CX43.

Methods: The study included 151 primary colorectal carcinoma and 71 colorectal adenomas. The control group comprised 30 colon samples. Connexins were detected with immunohistochemistry.

Results: There was a lack of membranous distribution of connexins or a shift from moderately membranous immunoreactivity to predominantly cytoplasmic accumulation of CX32 and CX43 in studied colon tumors. Mentioned alterations were found in adenomas and augmented in cancer. Expression of Cx32 was significantly associated with grading of colorectal cancer, implicating a role of intracellular CX32 in regulation of tumor growth and differentiation. A strong correlation was present between CX32 and CX43 in node-positive cases and absent from node-negative ones.

Discussion/Conclusion: To our knowledge, our study is the first illustration for a gradual loss of functional gap junctions within progression of colorectal neoplasia. An intracellular location of connexins, the site of their common and the most frequent detection within cancer cells in our study may be of significance. Independently of its role in functional gap-junctions, cytoplasmic CX32 could be involved in cancer differentiation, resulting in a higher rate of CX32 positive moderately differentiated tumors (G2) than poorly differentiated CX32-positive ones (G3).
Tubulo-villous colorectal adenocarcinoma vs. mucin and signet-ring cell carcinoma – Is there a prognostic difference?

Markus Doß, M.D.\textsuperscript{1}; Ulrich Nitsche, M.D.\textsuperscript{1}; Matthias Maak, M.D.\textsuperscript{1}; Tibor Schuster, M.Sc.\textsuperscript{2}; Rupert Langer, M.D.\textsuperscript{3}; Helmut Friess, M.D.\textsuperscript{1}; Robert Rosenberg, M.D.\textsuperscript{4}

\textsuperscript{1}Chirurgische Klinik und Poliklinik, Klinikum rechts der Isar, Technische Universität München; \textsuperscript{2}Institut für medizinische Statistik, Klinikum rechts der Isar, Technische Universität München; \textsuperscript{3}Institut für Pathologie und pathologische Anatomie, Klinikum rechts der Isar, Technische Universität München, Germany; \textsuperscript{4}Chirurgische Klinik, Kantonsspital Baden, Switzerland

**Introduction:** Our guidelines do not recommend different therapy of colorectal carcinoma in dependency of histopathological subtype. High volume studies investigating the clinical and prognostic significance of histopathological subtype of colorectal carcinoma are missing in the European area.

**Methods:** We analyzed data of 2868 patients with colorectal carcinoma, which underwent surgery in our hospital between 1982 and 2007. Clinical and histopathological parameters were collected in a prospective documented databank. Either univariate or multivariate analysis in dependency of histopathological subtype (tubulo-villous adenocarcinoma, mucinous or signet ring cell carcinoma) was conducted. Median follow-up of patients was 52 months.

**Results:** 2482 patients with tubulo-villous adenocarcinomas (86.5%), 357 patients with mucinous subtype (12.5%) and 29 patients with signet ring cell carcinoma (1.0%) underwent surgery.

Mucinous and signet ring cell carcinomas were noted to have a higher incidence of right-sided lesions (67.1% bzw. 76.5%; $p < 0.001$) in contrast to tubulo-villous adenocarcinoma. The incidence of signet ring cell carcinoma was higher in younger patients ($p < 0.001$). Regarding UICC-classification statistical distribution showed significant higher number of patients with advanced cancer stages (UICC III and IV) when mucinous and signet ring cell carcinomas are analyzed ($p < 0.001$ bzw. $p = 0.003$). Furthermore local lymph node metastasis, distant metastasis and local lymphatic vessel invasion was more likely in signet ring cell carcinoma compared to tubulo-villous adenocarcinoma ($p < 0.001$). With regard to these criterias there was no significant correlation for mucinous carcinomas ($p = 0.062$).

5-year survival rates were significant lower ($p < 0.001$) in patients with mucinous and signet ring cell carcinomas (61.8% and 23.2%) in contrast to 5-year survival rates of patients with tubulo-villous adenocarcinomas (68.3%). Signet ring cell carcinomas turned out to be an independent prognostic factor in multivariate analysis (HR 2.4, 95% CI: 1.5–3.6; $p < 0.0001$), whereas mucinous carcinomas did not ($p = 0.118$).

**Discussion/Conclusion:** Mucinous and signet ring cell carcinomas reveal a different tumor biology in contrast to adenocarcinomas. Especially signet ring cell carcinomas represent a high risk group because of low survival rates.
High myeloperoxidase positive cell density in colorectal cancer is an independent favorable prognostic factor

Raoul A. Droeser*1,4, Christian Hirt*1,4, Serenella Eppenberger-Castori2, Inti Zlobec3, Carsten T. Viehl1, Daniel M. Frey1, Raffaele Rosso6, Giandomenica Iezzi4, Giuseppe Sconocchia5, Giulio Spagnoli4, Michael Heberer4, Alessandro Lugli3, Luigi Terracciano2 and Daniel Oertli1
1Department of Surgery, University Hospital Basel, Switzerland
2Institute for Pathology, University Hospital Basel, Switzerland
3Institute for Pathology, University Hospital Bern, Switzerland
4Institute for Surgical Research and Hospital Management ICFS, Basel, Switzerland
5Institute of Translational Pharmacology, National Council Research, Rome, Italy
6Department of Surgery, Ospedale Regionale di Lugano, Switzerland

Introduction: Factors of the innate and adaptive immune system seem to play a major role in prognosis of colorectal cancer (CRC). Nevertheless, the prognostic role of granulocytes in CRC remains unclear. Therefore, we investigated the prognostic impact of the granulocyte markers myeloperoxidase (MPO) and CD15 in CRC.

Methods: Tissue microarrays composed of 1420 CRCs were immunostained with MPO and CD15. The number of MPO and CD15 positive immune cells in the tumor microenvironment was counted and correlated with patients’ clinico-pathological features. To further characterize the MPO and CD15 positive cell population, flow cytometric analysis of fresh tumor tissue was performed. In vitro, two CRC cell lines were coincubated with granulocytes, and growth inhibition was assessed.

Results: A high density for MPO and CD15 positive cells could be found in 14.5% and 10.7% of tumor samples, respectively. High MPO and CD15 positive immune cell density was significantly associated with a better overall survival (p = 0.003, and p = 0.050, respectively). The number of MPO positive cells closely correlated with CD15 positive cell infiltration (p < 0.001; r = 0.75). In a multivariate analysis including age, gender, T stage, N stage, vascular invasion, tumor border configuration and microsatellite stability, MPO density was an independent prognostic marker (p = 0.020), but not CD15 (p = 0.500). In flow cytometric analysis MPO positive cells expressed CD15, CD16 and CD66b, but were negative for HLA-DR. Granulocyte coincubation with two CRC cell lines showed growth inhibition of 70% (SD: ± 4–11).

Discussion/Conclusion: High density of myeloperoxidase positive cells is an independent favorable prognostic factor in CRC patients.

*These authors contributed equally to the study.
Postoperative outcome and long-term survival after laparoscopic assisted right hemicolecotomy during the learning curve: A case-matched analysis with open approach

Traian Dumitrascu, Catalin Vasilescu, Victor Tomulescu, Mihnea Ionescu, Irinel Popescu
Fundeni Clinical Institute, Center of General Surgery and Liver Transplantation, Bucharest, Romania

Introduction: Laparoscopic surgery has been proven as safe for colonic pathology, with certain advantages. However, most of the quality studies are coming from centers with high expertise in laparoscopic approach. Achievement of expertise in the laparoscopic colo-rectal surgery remains a major concern. The aim of the study is to present the early and late postoperative outcome after laparoscopic assisted right hemicolecotomy during the learning curve.

Methods: The first 49 patients with laparoscopic assisted right hemicolecotomy performed at Fundeni Clinical Institute, Bucharest were matched with 49 open right hemicolecotomies performed during the same period of time.

Results: There were no differences between the two groups regarding the mortality and morbidity rate. From oncological point of view there were no differences regarding the number of harvested lymph nodes or distance from tumor to the nearest edge. Median operative time was significantly higher in the laparoscopic group (p < 0.0001); however, with time there were no significant differences. In the laparoscopic group the median intraoperative blood loss (p < 0.001) and median hospital stay (p = 0.002) were significantly lower. Median follow-up was 88 months. There were no differences in median survival between the two groups (p = 0.753) for patients with malignant pathology.

Conclusion: Laparoscopic assisted right hemicolecotomy is a safe procedure even when the learning curve is not reached. Moreover, the advantages of the laparoscopic approach start during the learning curve. Nevertheless, the oncological radicality and long-term survival is not jeopardized by the learning curve.
Risk factors for adverse outcome of emergent colon cancer surgery

S.K. Faes, A. Schnider, M. Weber
Department of Surgery, City Hospital Triemli, Zurich, Switzerland

Objective: Approximately 20% of colon cancer patients present with conditions requiring emergent operative resection. Emergencies are associated with higher ASA score, advanced tumor stages and higher morbidity and mortality. The aim of this study was to identify risk factors for this adverse outcome and detect subgroups at particular risk.

Methods: All patients requiring operative resection for adenocarcinoma of the colon between 01/01/2000 and 12/31/2009 were reviewed and allocated to the emergent (n = 124) or elective (n = 529) group. The outcome factors mortality, complication score, positive lymph node number (PLN) and lymph node ratio (LNR) were analyzed. We tried to explain the significant differences found by adjusting for possible confounders (BMI, age, tumor stage, ASA score and preoperative weight loss). This could be investigated via logistic regression. Different emergency causes (perforation, obstruction, bleeding) were separately analyzed to identify high-risk conditions.

Results: In the logistic regression of mortality with emergency as explanatory variable we had a significant odds-ratio (OR) of 3.045. When introducing the possible confounders this OR dropped to 2.37, being still slightly significant. Age and ASA score were significant in this model. Analysis of complication score revealed a significant OR of 2.16. When introducing the confounders the OR dropped to 1.84, ASA score was the only significant confounder. The OR for PLN was significant and did not decrease after adjustments. Age was the only significant confounder. In a linear regression for LNR we obtained a significant mean difference (MD) of 0.045. After adjustments this MD dropped to 0.034, BMI was a significant confounder.

Looking at emergent conditions with perforation and obstruction simultaneously, we saw an adverse outcome for morbidity (p = 0.014) and mortality (p = 0.023) compared to other emergent presentations.

Conclusion: Higher ASA score and age displayed to be risk factors for adverse outcome in emergent patients. The adverse outcome could not entirely be explained by confounders. The emergency itself remained to be the strongest predictor for adverse outcome, this was especially true for perforated and obstructing tumors. There is an urgent need to further evaluate emergent operations, analyze factors responsible for adverse outcome and decrease prevalence of emergencies.
Ulcerative colitis as a risk factor for colorectal cancer

Olga V. Fedorova, Elvira N. Fedulova, Olga A. Tutina, Olga V. Shumilova
FGU R&D Institute of Children’s Gastroenterology, Nizhny Novgorod, Russia

Colorectal cancer (CC) accounts for almost ten percent of all cancer deaths.

Introduction: Individuals with UC are at increased risk of developing CC. The most significant risk factors for CC in patients with UC are the duration of the disease, extent of inflammation in the colon, PSC, early age of onset, the presence of CC in the family history and a lack of folic acid, inadequate medical therapy. The most significant predictor of the risk of malignancy in patients with IBD is the presence of dysplasia in colonic biopsies.

Methods: Serum tumor markers, including carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA 19-9), alpha-fetoprotein (AFP), and tissue polypeptide-specific antigen (TPS), may be helpful in the early diagnosis of CC, in the initial assessment of the extent of the disease (aggressiveness, metastases), and in monitoring tumor growth or regression during treatment. We also determined low and medium molecular weight peptides (LMMWP – universal markers of intoxication) and OP (oligopeptides) in erythrocytes, plasma and urine.

Results: Histological detection of colon dysplasia is considered the high-risk CC and in more 40% of cases associated with the presence of invasive carcinoma. High probability of malignant transformation in patients with total UC. The features of CC in patients with UC are a poorly differentiated malignant forms, multiple and rapid metastasis, extensive destruction of the colon tumor.

Discussion/Conclusion: The course of treatment for CC is largely determined by the stage of the cancer. Possible treatments include surgery, chemotherapy, radiation therapy, radiofrequency ablation (RFA), vaccines, and immunotherapy. Prolonged use mesalazin (Salofalk®) significantly (80%) reduces the risk of CC in patients with UC. For the prevention of colorectal cancer patients also have long-term use of UDCA (Ursofalk®) and cytoprotector (Mucofalk®).
IBD: Cytoprotection for the prevention of colorectal cancer

Olga V. Fedorova, Elvira N. Fedulova, Olga A. Tutina, Olga V. Shumilova
FGU R&D Institute of Children’s Gastroenterology, Nizhny Novgorod, Russia

Colorectal cancer (CRC) is in the 4th by frequency among all forms of cancer and is in the 2nd by causes of death associated with cancer after lung cancer in the world.

Introduction: Individuals with UC are at increased risk of developing colorectal carcinoma, particularly if there is long-standing disease or extensive colitis. UC observed 8.8–23-fold increased risk of developing CRC. The risk of CRC does not begin until 8 to 10 years after the time of diagnosis of UC. Thereafter it increases by approximately 0.5% to 1.0% per year. The cumulative risk of developing of CRC over 25 years is 9–34% (with UC with PSC – up to 50%). Early onset (before age 15) is an additional risk factor. In patients with Crohn’s disease, the risk of malignancy is smaller and less well defined. The most significant predictor of the risk of malignancy in patients with IBD is the presence of dysplasia in colonic biopsies.

Methods: In accordance with standards complex therapy of the given children’s diseases includes enterosorption.

Results: Enterosorbent Enterosgel is of porous structure in the form of solid, spatially formed silicon organic matrix with specified pore dimensions, which preferentially secure the sorption of middle-molecule substances. Enterosgel has selective sorption (does not reduce absorption of vitamins, microelements and Ca, enzymes, slgA) and detoxication properties, thus reducing toxic load on natural detoxication systems and the risk of development of infectious and autoimmune complications. It has an organic nature and high biocompatibility with intestine tissues, it has hydrophobic surface. It protects cell surface of the mucous membrane of the stomach against aggressive attacks and provides absorption of ulcerative destruction products, which prevent adequate epithelization and improvement of morphofunctional state of the intestine wall. Cytoprotective properties of the preparation are stipulated by restoration of the intestinal barrier accompanied by increase of slgA secreted by cells of the mucous membrane of the intestine, restoration of the structure of the microcirculatory race and positive morphologic dynamics. Enterosgel is completely harmless and in contrast to other sorbents does not cause damages to the mucous membrane of the gastrointestinal tract and may be administered protractedly (within several months) without causing atony of the intestine. Enterosgel creates comfortable conditions for development of the normal microflora and improvement of the microbiological landscape of the intestine.

Discussion/Conclusion: Through the sorption of toxic products of the life activities of microflora, which damage the epithelium of the gastrointestinal tract, and through the sorption of deficient metabolism products, Enterosgel creates ideal conditions for mucosal regeneration. Apparent clinic efficiency with the distinct cytoprotective effect enable to recommend Enterosgel for wide application with children with IBD as medication for sorption efferent therapy and for the prevention of CRC.
HER-2/neu immunoexpression in colorectal and gastric carcinomas

O. Fratila¹, Tiberia Ilias¹, M. Puscasu¹, Romeo Mihaila²
¹University of Oradea, Romania; ²“Lucian Blaga” University, Sibiu, Romania

Introduction: Amplification of HER-2/neu oncogene became a biomarker for identifying patients responding to HER-2 targeting therapy using trastuzumab (Herceptin), especially in breast cancers. The role of HER-2/neu in other cancers is less well established.

Methods: The aim of our paper was to assess HER-2/neu expression in colonic and gastric carcinomas and its relationship to clinic-pathological parameters. Forty patients undergoing surgery at for advanced digestive carcinomas were evaluated. 20 colorectal and 20 gastric specimens were H&E stained and divided into 3 subtypes: intestinal adenocarcinoma, diffuse carcinoma, mixed and other variants. HER-2/neu immunohistochemistry was performed with Hercep-Test Kit according to manufacturer's recommendations. Evaluation was performed using a semi-quantitative method (score 0–3+) and scores 0 regarded as HER2/neu-negative, scores 1+, 2+ and 3+ as positive.

Results: The 20 colonic cancers were 12 intestinal adenocarcinomas and 8 diffuse carcinomas. The 20 gastric cancers were 9 intestinal adenocarcinomas, 9 diffuse carcinomas and 2 other histological type. Among positive tumors, 2 were colonic (rectum) and 5 gastric. The immunohistochemical staining revealed 33 Her-2/neu negative and 7 Her-2/neu positive samples, out of which 5 were slightly positive/1+ (3 gastric cancers-1 poorly differentiated intestinal adenocarcinoma, 2 diffuse carcinoma – and two colonic intestinal adenocarcinoma) and 2 were moderately positive/2+ (high grade gastric intestinal adenocarcinomas). Overexpression of HER-2/neu was not associated with gender, age at diagnosis, or site of primary tumor.

Discussion/Conclusion: In our study the moderately positive HER-2/neu stained specimens were observed in advanced high grade intestinal gastric carcinoma, but not in the same histological subtype of colorectal cancer. Her-2/neu staining appears to be a promising marker for increasing cure rates especially in gastric cancer. Further studies are needed to see if colonic adenocarcinomas might be as well routinely stained with Her-2/neu.
Oct4, spliced variant OCT4B1, a novel marker for human colorectal cancer

Maria Gazouli¹, George E. Theodoropoulos², Maria G. Roubelakis¹,³, Anna Vaiopoulou¹, Joanna Papailiou², Nikolaos Nikiteas⁴, Nicholas P. Anagnou¹,³
¹Department of Basic Medical Research, Laboratory of Biology, School of Medicine, University of Athens, Athens, Greece; ²First Department of Propaedeutic Surgery of Athens Medical School, Hippocration University Hospital, Athens, Greece; ³Cell & Gene Therapy Laboratory, Biomedical Research Foundation of the Academy of Athens, Greece; ⁴Second Propaedeutic Department of Surgery, Laiko Hospital, School of Medicine, University of Athens, Athens, Greece

Introduction: OCT4, a POU-domain transcription factor is considered to be a key factor in maintaining the pluripotency of stem cells. Several OCT4 isoforms are differentially expressed in human pluripotent and non-pluripotent cells. Reactivation of OCT4 expression is postulated to occur in differentiated cells that have undergone tumorigenesis. To examine OCT4 expression in colorectal cancer (CRC) tissues, and to assess the efficacy of OCT4 as a potential biomarker for CRC, in this study, we investigated its expression in CRC tissues, evaluated its relationship to various clinicopathological parameters and defined the isoform of OCT4 that was found to be expressed in CRC cases.

Methods: Primary tumor tissues and matching adjacent non-cancerous tissues were obtained from 84 CRC patients. OCT4 expression and isoform determination were documented by reverse transcription-PCR and real-time PCR. OCT4, Sox-2, and NANOG localization were performed using immunohistochemistry. The isoforms expressed in the studied cases were confirmed by sequencing. Twenty biopsy specimens representing healthy tissues, retrieved from colonoscopy were studied in parallel as controls.

Results: OCT4 expression levels were higher in CRC tissues compared to matching, adjacent non-cancerous tissues, and healthy controls. Additionally, the levels of OCT4 expression in CRC tissues correlated with tumor stage. OCT4 and Sox-2 were localized in the nuclei and the cytoplasm of CRC cells. In all CRC cases, we found that the OCT4B1 isoform is expressed. Over-expression of OCT4B1 was found in poorly and moderately differentiated CRC tissues.

Conclusions: In conclusion, the data imply that OCT4B1 isoform may represent a potential biomarker for the initiation, progression, and differentiation of CRC.
Assessment of the local recurrence rates of colorectal cancer after curative resection

Amelia Genunche-Dumitrescu, D. Badea, M. Badea, P. Mitrut, A. Badea
University of Medicine and Pharmacy, Clinical Hospital of Emergency, Craiova, Romania

Introduction: Aim of this study was to assess the recurrent rate of colorectal cancer after surgery treatment. Also, we aim to detection a posible relationship between recurrence rates and other parameters.

Methods: We studied 156 patients with colorectal carcinoma from Emergency Clinical Hospital Craiova. We monitor the evolution of disease and the risk of recurrences after surgical treatment at 6, 12, 24 and 36 months. The examination was based of clinical manifestations, colonoscopy with biopsy criteria. Statistical analysis use Wilcoxon and Kruskal-Wallis test.

Results: A percent of 56.41% (88 cases) of the patients with colorectal cancer (52 males and 36 females) underwent surgical treatment. The type of adenocarcinoma was: papillary in 15 cases, tubular (49 cases), mucinous (12 cases), villous (5 cases) and undifferentiated (7 cases). Most of those patients had Duke’s B stage (38 cases) or C stage (34 cases) tumors. The localization of carcinoma was: right colon 19 cases, transverse colon 7 cases, left colon 13 cases, sigmoid 20 cases and rectum 29 cases. The 38 patients had cancer recurrences: 3 patients after 6 months, 9 patients after one year, 16 patients after 24 and 10 patients within 36 to 40 months. All recurrences in patients with initial stage I disease were local and regional, where 14 of 19 recurrences in stage II disease were distant. Two recurrences were detected at six patients during separate examinations and three recurrences in two patients in one examination. Local recurrence occurs more frequently in sigmoid (55.0%) and rectal cancers (62.07%). Lower stage was associated with higher adenoma recurrence rates p = 0.04. Factors including age, sex and clinical manifestations were not significantly correlated with recurrence rates.

Discussion/Conclusion: Local recurrence occurs more frequently in sigmoid and rectal carcinoma. The rate of recurrence was correlated with Duke’s stage. The routine colonoscopy is capable of early tumor detection.
The contribution of major etiologic factors to the risk of colorectal cancer

Amelia Genunche-Dumitrescu, D. Badea, M. Badea, P. Mitrut
University of Medicine and Pharmacy, Clinical Hospital of Emergency, Craiova, Romania

Introduction: The aim of this study was to investigate the prevalences of risk factors that develop colorectal carcinoma (CRC).

Methods: We studied 133 patients with colorectal carcinoma examined and endoscopic diagnosed in Clinical Hospital of Emergency Craiova. The diagnosis was based of clinical manifestations, colonoscopy with biopsy criteria.

Results: The type of adenocarcinoma was: papillary (27 cases), tubular (69 cases), mucinous (17 cases), villous (9 cases) and undifferentiated (11 cases). Most of these patients had Duke’s B stage (62 cases) or C stage (54 cases) tumors. The risk factors for develop CRC was: polyps (72 cases), dietary lipids (53 cases), inflammatory bowel disease (28 cases), radiotherapy (11 cases), familial adenomatous polyposis (4 cases), physical inactivity (56 cases) and unknown causes (45 cases). In 58.66% of cases (78 patients) two or more risk factors of CRC was associated. CRC was developed in 4 patients with Crohn’s disease (CD) and in 24 patients with severe ulcerative colitis (UC). Most of them (18 cases, 75%) had extensive colitis and 6 cases (25%) had subtotal lesions of colon. In 91.66% of cases (22 patients), the duration of IBD was longer than 10 years. Majority of UC patients (17 cases, 70.8%) had pseudo-polyps of colon. In 11 cases, CRC developed after pelvic radiotherapy, used for: prostate cancer (2 cases), uterine and ovarian cancer (5 cases), Hodgkin’s disease (2 cases), bladder cancer (2 cases). The colorectal polyps seem to be transforming more often in dysplastic lesions at older people compared with younger patients. The risk of CRC was higher in patients with more polyps (63 cases).

Discussion/Conclusion: The risk CRC was developed in patients with long duration of UC, with severe forms, which was complicated with pseudo-polyps. Patients after pelvic radiotherapy are a greater risk for developing a CRC.
Correlation of prognosis and gene expression signatures in colorectal cancer

Jörn Gröne, Lucas Lee, Johannes Lauscher, Heinz J. Buhr
Chirurgische Klinik I, Campus Benjamin Franklin, Charité – Universitätsmedizin
Berlin, Germany

Introduction: In solid cancers gene expression profiling for prognosis prediction remains controversial. The aim of the study was to identify and to assess a prognostic gene expression signature for colorectal cancer (CRC) patients.

Methods: For the discovery and validation of the prognostic signature two public CRC microarray data sets (Gene Expression Omnibus sets) and an own generated data set (own set) were used. Own set was generated from laser microdissected tumor cryotissue and Affymetrix Gene Chip hybridization of 62 patients (29 colon & 33 rectal cancers; 13 UICC I, 21 UICC II, 23 UICC III, 5 UICC IV). For statistical analyses software package R was used.

Results: A signature of 112 coexpressed genes with prognostic value could be identified and validated. CRC patients with a low expression of the signature had a favorable prognosis (p = 0.011). Literature gene network analysis revealed an enrichment of direct transcriptional targets of c-myc, ESR1 and p53 among the signature genes.

Discussion/Conclusion: CRC patients with a more favorable prognosis could be separated from patients with a higher risk of recurrence by means of a 112 gene expression signature based on public and own data sets. The coexpressed genes seemed to be linked to proliferation and apoptosis possibly by regulation through c-myc, ESR1 and p53 and might be an alternative predictor of colorectal cancer prognosis.
Molecular biomarkers play a major role in the selection of treatment strategies in CRC

J. Gülden, A. Bogner, M. Joka, K.-W. Jauch, B. Mayer
Clinic of the University of Munich, LMU, Department of Surgery-GH, Munich, Germany

Introduction: CRC is still associated with high mortality. Aim of the present study is to get a better understanding of the predictive and resistance biomarkers, to select an individual therapy for each patient based on his specific biomarker profile.

Methods: Tumor and mucosa samples were analyzed from 49 CRC patients. Molecular biomarkers, including BRAF15 and KRAS, were identified by micro-dissection followed by DNA isolation, PCR and pyrosequencing. The mutation status was correlated with a panel of clinical and pathological factors. Patient spheroids were prepared from fresh tumor samples and treated with standard therapy. Most effective drugs were identified by FACS analysis.

Results: KRAS and BRAF mutations were not detectable in benign mucosa samples. Contrary 39% of the primary CRC revealed mutated KRAS. Specifically, G13D was found in 26.3%, G12V and G12D in 31.5% respectively and G12A in 10.5%. KRAS mutations significantly correlated with the mucineous tumor type (p = 0.014) and a strong Ki67 proliferation rate (p = 0.051). BRAF V600E mutations were present in 16% of the primary CRC and correlated with advanced tumor stage, namely pT3/4 (p = 0.001), pN1/2 (p = 0.047) and lymphangiosis carcinomatosa (p = 0.033). Cetuximab response in the spheroid model was obtained in a portion of KRAS wild type and G13D mutated primary tumors, but not in other mutation variants (p = 0.001).

Discussion/Conclusion: The BRAF V600E mutation seems to be a useful marker for progression in CRC.
KRAS G13D mutation is comparable to KRAS wild type and thus has to be considered in the treatment strategy of the individual cancer patient.
A genetic mouse model to identify the role of the immune adapter protein MyD88 in colon cancer

Anne Holtorf, Melanie Martini, Bernhard Holzmann, Klaus-Peter Janßen
Klinische Forschergruppe „Molekulare Tumorbioptologie“, Chirurgische Klinik und Poliklinik, Klinikum rechts der Isar der TU München, 81675 Munich, Germany

Introduction: Chronic inflammatory diseases of the intestine are causative and well documented triggers for colon carcinogenesis. However, the cellular and molecular mechanisms by which the immune system mediates the development and progression of colon cancer remain unclear. Myeloid-differentiation factor 88 (MyD88) is an adapter protein in Toll-like receptor and Interleukin-1 receptor signaling pathways. Previous studies highlighted a critical role for MyD88-mediated signaling in several types of solid cancers. Our genetic mouse model allows tissue-specific expression of Myd88, based on the Cre/loxP system, and therefore identification of the complex interaction between tumor and immune system during intestinal carcinogenesis.

Methods: Insertion of an “intron-gene-trap” flanked with loxP motifs into Myd88 leads to global inactivation of Myd88 expression (MyD88<sup>stp/stp</sup>). Breeding of MyD88<sup>stp/stp</sup> mice with LysMCre or villin-Cre mice leads to tissue-specific excision of the “intron-gene-trap” and therefore Myd88 expression is reactivated exclusively in either myeloid cells (MyD88<sup>MYEL</sup>) or intestinal epithelial cells (MyD88<sup>IEC</sup>), retaining endogenous regulation of gene expression. Subsequently, these animals were mated with established genetic mouse models for human colon cancer (villin-Kras<sup>V12G</sup> and Apc<sup>1638N</sup>).

Results: Global MyD88 deficiency significantly decreased development of intestinal tumors, induced by either oncogenic KRAS or loss of function of Apc. Re-expression of MyD88 in intestinal epithelia and tumor cells partially restored tumor growth. Preliminary data indicate that exclusive Myd88 expression in myeloid cells triggers tumor development comparable with parental Apc<sup>1638N</sup> mice.

Discussion/Conclusion: Analysis of this new mouse model will enable us to identify the role of MyD88-mediated signaling in defined cell populations, and to further elucidate its influence on tumorigenic processes.
Colorectal cancer assessment in a group of patients from the western part of Romania

Tiberia Ilias¹, O. Fratila¹, Dana Puscasu²
¹University of Oradea, Romania; ²Emergency Clinical County Hospital, Oradea, Romania

Introduction: The complete and correct diagnosis of colorectal cancer is possible mostly as a direct result of using videoendoscopy and having the possibility of taking colonic biopsies.

Methods: The aim of our paper was to assess and correlate the endoscopic and histopathological parameters of malignant colorectal tumors of 171 patients diagnosed between 2008 and 2010 in the Endoscopy Unit of the 3rd Medical Clinic from Oradea, Romania. We retrospectively studied the epidemiological parameters (gender, age, social environment), the morphologic features and the site of the lesions identified during endoscopy as well as the histopathologic characteristics, using WHO grading system.

Results: From a total number of 1996 patients who underwent endoscopy, 163 (8.2%) were diagnosed with different histopathological types of colorectal cancer and 16 cases with premalignant lesions (mild/severe dysplasia). Our data pointed out that male gender (63%), urban environment (64%) and age over 50 years (70%) prevailed. The left colon (77%) and the fungating appearance (47%) were frequently encountered. In the majority of the cases we identified invasive carcinomas (84.5%): intestinal adenocarcinoma (134 cases – 82%) and „signet ring cells” carcinoma (4 cases -2.5%). The grading of the adenocarcinomas showed: G-I: 89 cases (66%), G-II: 40 cases (30%), G-III: 5 cases (4%).

Discussion/Conclusion: The frequency of colorectal cancer in western Romania is relatively high. Male gender prevailed in our study, unlike literature data which indicates similar incidence rates in men and women as well. Growing old and urban environment turned out to be risk factors in the development of the disease. The majority of the patients in our study had rectosigmoidian cancers, polypoid-stenotic forms. The adenocarcinoma was the most frequent histological form. These remarks correlate the features of colorectal cancer in patients from western Romania to other geographic areas in our country.
Inflammatory response related gene polymorphisms and colorectal cancer

G. Karamanolis, G. Theodopoulos, M. Gazouli
Athens Medical School, Athens, Greece

**Aim:** To investigate the association between common single nucleotide polymorphisms (SNPs) in inflammatory response-related genes such as interleukin (IL)-6, IL-8, tumor necrosis factor α (TNFα), peroxisome proliferators-activated receptor γ (PPARγ), intercellular adhesion molecule-1 (ICAM-1) and the risk of colorectal cancer (CRC) in a group of Greek patients.

**Methods:** The study group consisted of 222 CRC patients and 200 healthy controls. Genotyping was performed using allele-specific PCR of PRC-RFLP and the results were confirmed by sequencing. We studied the association of SNPs in the IL-6 (-174G > C), IL-8 (-251T > A), TNFα (-308G > A), ICAM-1 (R241G and K469E), and PPARγ (Pro12Ala) genes and the risk of CRC.

**Results:** The IL-6-174G, R241 and K469 alleles of ICAM-1 were associated with increased risk of CRC (OR = 1.77, 95% CI: 1.34–2.34; OR = 1.83, 95% CI: 1.23–2.72; and OR = 1.35, 95% CI: 1.03–1.77 respectively). The IL-8 and TNFα polymorphisms had no effect. Whereas the PPARγ Pro12 genotype was associated with increased risk of disease (OR = 1.78, 95% CI: 1.25-2.49).

**Conclusion:** The association between common SNPs in immunologic response-related genes and CRC is reported in the present study. Apart from shedding light on the mechanisms of malignancy initiation and progression, SNPs may improve appropriate screening for sub-populations at risk.
Laparoscopic surgery for rectal cancer

S. Kathy, D. Tóth, Z. Kincses
Department of General Surgery, Kenézy Teaching Hospital of Medical and Health Science Centre of University of Debrecen, Debrecen, Hungary

Introduction: Laparoscopic surgery nowadays widely used for the treatment of rectal cancer. Besides the well known benefits of laparoscopic methods, lately, data shows equivalent results compare with open resections regarding oncologic and long-term outcomes too. Our aim was to evaluate our experiences with laparoscopic resections for rectal cancer.

Methods: From 2005 to 2011 at our institution 122 laparoscopic colorectal operations were performed. 43 were operated for rectal cancer. Most patients received neoadjuvant therapy. 32 patients had laparoscopic rectal resection, 11 patients had laparoscopic abdominoperineal resection. Data of treatments were collected and evaluated.

Results: The median age of these patients was 62 years (range, 37–81). Intraoperative complications were at 3 cases (6.9%): 2 bleeding, 1 ureter lesion. Postoperative surgical complications developed in 3 patients (6.9%): 1 anastomosis bleeding, 2 wound healing disturbance. Anastomotic leak wasn’t occured. Conversion to open surgery was required in 5 patients (11.6%). The reasons were: 2 bulky tumor, dense adhaesion in 1 case, complications of anaesthesia in 1 case. There was no port-site metastasis. Median length of postoperative hospital stay was 4.7 (4–12) days. There was no mortality.

Discussion/Conclusion: Laparoscopic surgery for rectal cancer safe and feasible technique with good surgical results. It has low complication rate, rapid intestinal recovery, short hospital stay, and no compromise of oncological outcomes.
CXC-chemokines as crucial immune mediators in colorectal carcinogenesis

Larissa Keller, Dietrich Doll, Cornelia Ochs, Klaus-Peter Janssen
Department of Surgery, Klinikum rechts der Isar, Technische Universität München, Munich, Germany

Introduction: Tumor progression and development are influenced by the tumor microenvironment and the immune system.

Methods: In order to identify crucial regulatory factors involved in this process, we previously analyzed 2 different patient groups with colon cancer (T3N0M0, R0 resection), one with good (survival > 5 years post operation, n = 25) and one with bad prognosis (patients died within 5 years after surgery, n = 25), by microarray analysis. The results of the microarray analysis were confirmed independently by qRT-PCR on 132 patient samples of all tumor stages. By ELISA and immunohistochemistry, we could identify cancer cells as main producers of the CXC-chemokines within colon tumors. To find out if the high intratumoral CXC-chemokine expression and T-cell infiltration were cause or consequence of the good prognosis, orthotopic and genetic mouse models were established. An orthotopic model based on an isogenic mouse rectalcarcinoma cell line, engineered to express CXC-chemokines, was established. These cells were implanted in the colon of immunocompetent or immunodeficient hosts.

Results: Interferon-regulated CXC-chemokines showed a significantly different expression, a high expression of chemokines was correlated with a good survival rate. The Interferon-regulated CXC-chemokines are soluble factors of the immune system and responsible for T-cell recruitment, as well as for inhibition of angiogenesis. Importantly, significantly more intratumoral CD8^+ effector and CD4^+ helper T^H1 T-cells were observed in tumor tissue with high CXC-chemokine expression. This is in accordance with reports stating that high intratumoral T-cell numbers are correlated with good prognosis.

Discussion/Conclusion: This analysis will allow us to investigate tumor formation and T-cell recruitment, depending on CXC-chemokine expression.
The risk factors of colorectal cancer operations

Z. Kincses, T. Csobán, S. Kathy, D. Tóth
Department of General Surgery, Kenézy Teaching Hospital of Medical and Health Science Centre of University of Debrecen, Debrecen, Hungary

Introduction: One of the most dangerous complications of colorectal surgery is suture insufficiency. The possibilities for precise diagnosis, the preoperative neoadjuvant treatment, the well-developed operating technique and the modern equipment have made it possible to reduce the degree of occurrence of postoperative complications. In spite of all these, in 3–25% of the cases, suture insufficiency occurs. Our aim was to examine the reasons for suture insufficiency.

Methods: At our department, from 2008 to 2010, 537 operations performed for colorectal cancer were analyzed from aspect of suture insufficiency. The complications can be grouped in many different ways according to the literature. The most popular is the Clavien-Dindo classification, which differentiates minor and major complications. There are factors, which are unquestionable. These are the following: the sex of the patient (male), smoking, the distance of the anastomoses, the size of the tumor, the diverting ileostomy and the drainage. The questionable factors are the following: preoperative radiotherapy, types of anastomoses, mobilization of the left flexure, blood-transfusion, BMI, diabetes mellitus and nutrition condition. These factors were evaluated.

Results: In our study the rate of complication after 537 colorectal cancer cases and the rate of suture insufficiency are in accordance with the literature. Besides the known and accepted risk factors, in our study, the nutrition condition, diabetes mellitus and the absence of mobilization of the left flexure were noted as risk factors of suture insufficiency. The occurrence of post-operative suture insufficiency was higher for smoking patients, male patients with large tumors and the anastomotic distance from the sphinter and the absence of diverting ileostomy.

Discussion/Conclusion: We believe that the standardized operating technique, the thorough preoperative examination and the careful preoperative preparation (nutrition) have great significance in the successful outcome of the operation.
Importance of the long-term surveillance of patients with ulcerative colitis considering the occurrence of dysplastic changes and colorectal carcinoma

M. Konecny, V. Prochazka, J. Ehrmann
2nd Internal Clinics of Gastroenterology and Hepatology of the University Hospital Olomouc, Czech Republic
Institute of Clinical and Molecular Pathology of the University Hospital Olomouc, Czech Republic

Introduction: Chronic course of idiopathic bowel disease manifests by recurring relapses with relatively high occurrence of complications, both intestinal and parenteral. The most serious complications include colorectal carcinoma (CRCa) in patients with long-term ulcerative colitis (UC) of extensive type.

Methods: In 1995–2010, 74 patients with UC of extensive type lasting longer than 10 years were observed within the treatment programme of the 2nd Internal Clinics of the University Hospital Olomouc. In the whole set, colonoscopic examinations were carried out in regular two-year (or shorter) intervals with follow-up biopsy and histological examination focused on the occurrence of dysplastic changes and colorectal carcinoma.

Results: In 6 patients CRCa was found as a complication of long-term course of UC, in 42 patients. Dysplastic changes have been detected and their development and seriousness monitored in five-year periods. No statistically significant difference has been found (p = 0.11, p = 0.13, p = 0.09 respectively). In 26 persons, no dysplastic changes have been found during the whole period of observation.

Discussion/Conclusion: Regular colonoscopic examinations should be commenced within 10 years from the date when the UC of extensive type was found. If no dysplastic changes are found by biopsy, we continue in endoscopic examinations in two-year intervals. When dysplasia of low grade is found, we perform another colonoscopy with the follow-up biopsy within one year. If the DALM type of macroscopic lesion or a stricture is found, colectomy is indicated. High-grade dysplasia is also an indication for colectomy as CRCa is found in the resectate in 40% of cases.
Identification of prognostic factors for long-term survival in stage IV colorectal cancer patients

B. Künzli¹, U. Nitsche¹, M. Maak¹, R. Gertler¹, G. Ceyhan¹, T. Schuster², C. Meyer-zum-Büschenfelde¹,³, H. Friess¹, R. Rosenberg¹
¹Chirurgische Klinik und Poliklinik, ²Institut für Medizinische Statistik und Epidemiologie, ³Ill. Medizinische Klinik, Klinikum rechts der Isar, Technische Universität München, Munich, Germany

Introduction: Therapeutic options in metastatic colorectal cancer have improved over the past decades. The aim of our study was to evaluate the prognostic capability of clinical, surgical and histopathological parameters in stage IV colorectal cancer patients who had undergone resection of their primary tumor.

Methods: Between 1982 and 2006, 639 consecutive patients with UICC stage IV colorectal cancer were treated with tumor resection followed by systemic chemotherapy. Clinical, histopathological and follow-up data were investigated.

Results: 128 patients (20%) underwent multivisceral resection. Resection of liver metastases was performed in 108 patients (17%). Local R0 and total R0 status was achieved in 509 patients (80%) and 101 patients (16%), respectively. The median cause-specific survival increased continuously from 10 (95% CI: 8–12) months for patients treated in the first years to 23 (95% CI: 19–27) months for those treated in the last five years of the study period. Median cause-specific survival for total R0 resected patients was 41 (95% CI: 32–50) months. Multivariable analysis identified patients’ age, pN, cM1a/b, R status and the date of resection of the primary tumor as independent prognostic factors.

Discussion/Conclusion: As oncological treatment options for stage IV colorectal cancer developed in the past decades, prognosis improved significantly. The identified prognostic factors help selecting M1 patients with potential long-term survival, who should undergo resection of the primary tumor and liver metastases followed by chemotherapy.
Initial results of a randomized controlled trial comparing clinical and pathological downstaging of rectal cancer after preoperative short-course radiotherapy or conventional chemoradiotherapy with delayed surgery

Tadas Latkauskas, Henrikas Pauzas, Paulius Lizdenis, Zilvinas Saladzinskas, Algimantas Tamelis, Dainius Pavalkis
Lithuanian University of Health Sciences, Kaunas, Lithuania

Introduction: The aim of this study was to compare the downstaging achieved after short-term radiotherapy (sRT) or chemoradiotherapy (chRT) followed by delayed surgery.

Methods: A randomized controlled trial of 83 patients with resectable stage II and III rectal adenocarcinoma. Forty six patients received long course chemoradiotherapy and 37 received short-term radiotherapy (5 x 5 Gy). Surgery was performed 6 weeks after preoperative treatment in both groups.

Results: The R0 resection rate was 91.3% in the chRT group and 86.5% in the sRT group (p = 0.734). Sphincter preservation rates were 69.6% vs. 70.3% (p = 0.342) and postoperative complications rates were 26.1% vs. 40.5% (p = 0.221). There were more patients with early pT stage (T0, T1) in the chRT group (21.8% vs. 2.7% p = 0.03) and more patients with T3 disease in the sRT group (75.7% vs. 52.2% (p = 0.036). There were no differences in pN stage, lymphatic and vascular invasion in either group. Pathologic downstaging (stage 0 and I) was observed in 8 (21.6%) patients in the sRT group versus 18 (39.1%) cases of chRT group, (p = 0.07). Tumors were smaller after preoperative ChRT (2.5 cm vs. 3.3 cm; p = 0.04).

Discussion/Conclusion: Long course preoperative chemoradiation resulted in statistically significant tumor downsizing and downstaging comparing with short term radiation, but there were no difference in the rates of R0 resection. Similar post operative morbidity was observed in both groups.
Radiofrequency-assisted hepatic resections metastases of colorectal cancer

A. Lavrinenko, V. Kashnikov, E. Rybakov, Y. Shelygin
State Research Center of Coloproctology, Moscow, Russia

Objectives: Intraoperative bleeding is a main obstacle for non-anatomic liver resection for colorectal cancer (CRC) metastases. The aim of prospective study was to evaluate safety and efficacy of hepatic metastasectomy of CRC origin using Habib™ 4X.

Methods: 55 patients with CRC liver metastases were operated on using Habib™ 4X in 2006–2011. Total number of resected metastases was 96 with median size of 2.2 ± 1.0 (0.5–6.0) cm.

Results: Mean intraoperative blood loss was 60 ± 24 ml, and average operative time was 50 ± 18 min. Mean resection margins of 0.9 (0.5–1.2) cm were achieved. There was no postoperative mortality. Three patients (5.0%) had collections, one of them required reoperative others were successfully treated by ultrasound-guided draining. All patients had adjuvant systemic chemotherapy XELOX. At median follow up of 14.0 ± 5.8 month, twelve patients relapsed and died because of cancer progression. 3-year actuarial survival reached 70.3 ± 11.7%

Conclusion: Radiofrequency assisted metastasectomy is safe and effective option for CRC liver metastases.
Neural invasion is not a prognostic factor in colon cancer due to missing neuro-cancer cell affinity

Florian Liebl¹, Ihsan Ekin Demir¹, Robert Rosenberg¹, Timo Kehl¹, Alexandra Boldis¹, Tibor Schuster², Matthias Maak¹, Karen Becker³, Rupert Langer³, Melanie Laschinger¹, Helmut Friess¹, Gürarp Onur Ceyhan¹  
¹Department of Surgery, Klinikum rechts der Isar, TU München, Munich, Germany  
²Institute of Medical Statistics and Epidemiology, Klinikum rechts der Isar der TU München, Munich, Germany  
³Institute of Pathology, Klinikum rechts der Isar der TU München, Munich, Germany

Introduction: Neural invasion (NI) is a neglected histopathological feature of colon cancer (CC). The slight clinical consideration may be due to the low prevalence of NI in CC compared to other gastrointestinal malignancies like pancreatic cancer (PCa). The aim of this study was to perform a comprehensive morphological and functional characterization of NI in CC and to assess its actual role in CC biology.

Methods: NI was detected in H&E-stained tissue sections of 673 patients with CC. The localization and the severity of NI was determined and related to patient’s prognosis and survival. To determine a potential affinity between CC cells (HT29, HCT-116) and neurons, a recently established in-vitro 3D-neural-migration assay was utilized, and the migratory behaviour of CC cells was compared to that of the PCa cell-line T3M4 via live-cell-imaging-analysis.

Results: NI was detected in 210 of 673 patients (31.2%). Although increasing NI severity scores were associated with a significantly poorer survival, multivariate analysis including gender, age, pTNM stage, grading, lymphatic invasion, CEA-level, resection status and tumor location did not reveal NI as an independent prognostic factor in CC. In the 3D migration assay, CC cells did not demonstrate any neurite-targeted migration behavior in contrast to the clearly observed one in T3M4 cells.

Discussion/Conclusion: NI is not an independent prognostic factor in CC. The lack of a considerable biological affinity between CC cells and neurons and the predominantly intraperitoneal localization of colon segments may explain the low prevalence and impact of NI in CC compared to PCa.
Systematic review and meta-analysis on the effect of preoperative radio(chemo)therapy on long-term functional outcome in rectal cancer patients

Martin Loos, M.D.¹, Philipp Quentmeier, M.D.¹, Tibor Schuster, Ph.D.², Ulrich Nitsche, M.D.¹, Ralf Gertler, M.D.¹, Andreas Keerl, M.D.³, Thomas Kocher, M.D.³, Helmut Friess, M.D.¹, Robert Rosenberg, M.D.¹,³

¹Department of Surgery, Klinikum rechts der Isar, Technische Universität München, Munich, Germany, ²Institute of Statistics and Epidemiology, Klinikum rechts der Isar, Technische Universität München, Munich, Germany, ³Department of Surgery, Kantonsspital Baden, Baden, Switzerland

Introduction: Preoperative radio(chemo)therapy (R(C)T) has been shown to significantly reduce the local recurrence risk and is therefore recommended in stage II and III rectal cancer. However, this multimodal treatment approach may be associated with late adverse effects. To determine the effect of preoperative R(C)T followed by total mesorectal excision (TME) on long-term anorectal, sexual and urinary function, we performed a systematic review and meta-analysis.

Methods: Pubmed, Embase and the Cochrane Library were searched for studies comparing functional long-term results after TME-optimized rectal cancer surgery with or without preoperative R(C)T.

Results: 27 studies (six randomized, eight prospective non-randomized and 13 retrospective case-control studies) including 7143 patients were identified. 15 of 18 studies, including all three randomized studies, demonstrated increased adverse effect rates of preoperative R(C)T on anorectal function. Meta-analysis revealed that stool incontinence occurred more often in irradiated patients (p = 0.0002) and manometric results were significantly worse after preoperative R(C)T (mean resting pressures [p = 0.04] and maximum squeezing pressures [p < 0.0001]). Ten of 11 studies, including all three randomized studies, demonstrated that preoperative R(C)T negatively affected male sexual function, but meta-analysis revealed no significance (p = 0.30). In females, one randomized multi-center trial demonstrated a negative influence of R(C)T on sexual function. Seven of nine studies and meta-analysis demonstrated no negative effect on urinary function (p = 0.82).

Conclusions: Current evidence demonstrates that, in contrast to urinary function, preoperative R(C)T negatively affects anorectal and sexual function. Functional disorders after multimodal rectal cancer treatment still represent a relevant clinical problem and should be followed more carefully.
Tumor targeting of gastrointestinal carcinomas with Shiga toxin B

Matthias Maak\textsuperscript{1}, Ulrich Nitsche\textsuperscript{1}, Ludger Johannes\textsuperscript{2}, Robert Rosenberg\textsuperscript{3}, Helmut Friess\textsuperscript{1}, Klaus-Peter Janssen\textsuperscript{1}

\textsuperscript{1}Chirurgische Klinik und Poliklinik des Klinikums rechts der Isar, TUM, 81675 Munich, Germany; \textsuperscript{2}CNRS-UMR 144, Institut Curie, 75248 Paris Cedex 05, France; \textsuperscript{3}Chirurgische Klinik, Kantonsspital Baden, 5400 Baden, Switzerland

Introduction: Tumor targeting is defined as the specific transport of molecules to a tumor for diagnostic or therapeutic purposes. A targeting vector should have molecular specificity, fast uptake in tumor cells, low immunogenic potential and the capacity to withstand degradation or inactivation. These requirements are satisfied by the non-toxic B-subunit of the bacterial Shiga toxin (STxB). The recombinant STxB is rapidly taken up into epithelial cells via the retrograde pathway. Moreover, the cellular STxB receptor, the glycosphingolipid Globotriaosylceramide (Gb3; CD77), is significantly over-expressed on a wide range of human carcinomas.

Methods: Colon carcinoma (n = 66), liver metastases (n = 11), healthy colon (n = 17) and liver (n = 5), pancreatic adenocarcinoma (n = 28) and matched pancreatic tissue (n = 27) were analyzed for Gb3 expression with thin layer chromatography. In parallel, immunohistochemistry on cryosections was performed, and uptake kinetics were tested with recombinant fluorescently labelled STxB on cancer cell lines (HT29, CaCo2, DLD1, MiaPaca2, BxPC3, DanG). The therapeutic use of STxB for the specific delivery of covalently coupled SN38, an active metabolite of the topoisomerase I inhibitor Irinotecan. The cytotoxic effect of the STxB-SN38 compound was tested on pancreatic and colorectal cancer cell lines.

Results: The Gb3 receptor expression is significantly increased in the tested carcinomas compared to healthy pancreatic tissue. Gb3 expression levels showed no correlation with survival or histopathology. By immunohistochemistry, we could recapitulate the biochemical findings, and found expression of Gb3 in tumor cells. STxB is taken up in cancer cells via the retrograde pathway within 60 minutes, and was detectable within the Golgi apparatus for up to 5 days. The cytotoxic effect of STxB-SN38 was found to be increased more than 100-fold as compared to Irinotecan. Moreover, this effect was effectively blocked by competing incubation with non-labeled STxB, demonstrating the receptor-specificity of the cytotoxicity.

Discussion/Conclusion: STxB has great potential as highly specific vector for tumor targeting on gastrointestinal carcinoma.
Colonoscopy screening markedly reduces the occurrence of colon carcinomas and carcinoma-related death

Christine N. Manser1,5, Lucas M. Bachmann2, Jakob Brunner3, Fritz Hunold4, Michael Fried1, Peter Bauerfeind1, Urs A. Marbet*5
1Division of Gastroenterology and Hepatology, Department of Internal Medicine, University Hospital, CH-8091 Zurich, Switzerland
2Horten-Center for Patient-Oriented Research and Knowledge-Transfer, University Hospital of Zurich
3Clinic for Gastroenterology, Cantonal Hospital of Glarus
4Gastroenterological Practice Canton Glarus
5Clinic for Gastroenterology, Cantonal Hospital of Uri, Altdorf, Switzerland

Introduction: Colonoscopy with possible polypectomy is an efficient and preferred screening method to reduce the incidence of colorectal cancer (CRC). However, critics argue that, to date, a reduction of incidence and mortality from CRC have not been demonstrated in a population setting.

Methods: A total of 1912 participants were screened and included along with 20,774 control patients aged 50 to 80 years in this population-based study. CRC cases were prospectively collected during the screening period of 1 and the follow-up period of 6 years in the complete screened and non-screened population. Follow-up data were corrected for negligible migration balance in the area. Tumor characteristics and risk or protective factors, age and gender, participation in general health screening examinations, history of CRC in a first-degree relative, smoking status, body-mass-index (BMI), frequency of sports activity, eating habits and patients' professions were recorded.

Results: Overall cancer incidence was significantly lower in the screened group compared to non-screeners (adjusted odds ratio 0.31; 95% CI: 0.16–0.59, p < 0.001). Tumor-associated mortality was also distinctly lower (adjusted odds ratio 0.12; 95% CI: 0.01–0.93, p = 0.04). Risk factors such as lifestyle, smoking, BMI as well as family history were similar in both groups. Blue-collar workers had a higher incidence of CRC compared to professionals. Risk factors for colorectal cancer were positive family history and smoking.

Conclusion: Colonoscopy with polypectomy markedly reduces CRC incidence and cancer-related mortality in the general population.
Complex pathology analysis of colorectal cancer in children

N.S. Marenich, A.S. Tertychnyy, D.M. Konovalov, A.G. Talalaev
Russian State Medical University, Moscow, Russia

Introduction: Carcinoma of the large bowel is rare in children and generally presents with advanced stages of disease. The histological type and possibly the developmental pathway of the tumors may differ from that in adults. The aim of this study was to draw the attention to this rare malignancy in children by reporting the diagnostic features of the three cases.

Methods: Three children (1 boy 14 years old [case 1] and 2 girls 8 [case 2] and 14 years old [case 3]) presented with non-familial large bowel malignancies. Formalin-fixed, paraffin-embedded material was available for review and additional immunohistochemical studies.

Results: All tumors occurred in the right colon and comprised rare histological types: adenosquamous carcinoma (case 1), medullary carcinoma (case 2) and poorly differentiated adenocarcinoma (case 3). All cancers were relatively well circumscribed and contained numerous intraepithelial and peritumoral lymphocytes. Classification by Dukes' staging demonstrated Stage C in all patients. We studied the tumors for hMLH1, hMSH2 or hMSH6 protein deficiency by immunohistochemistry. Loss of expression of MLH1 was identified in case 2 and loss of MSH6 expression in case 3, as demonstrated by loss of expression MLH1 or MSH6 in all tumor nuclei, consistent with mutational or transcriptional abnormalities.

Discussion/Conclusion: The pathology and immunohistochemical features in two of three of demonstrated cases of juvenile colon cancers appear consistent hereditary non-polyposis colorectal cancer (Lynch syndrome). These observations could have significant implications for management of children with colorectal cancer and testing of family members.
Microsimulation of colorectal cancer screening

Benjamin Misselwitz¹, Christine Manser¹, Luc Biedermann¹, Amnon Sonnenberg², Peter Bauerfeind¹
¹University Hospital Zurich, Zurich, Switzerland
²Oregon Health and Science University, Portland, OR 11772, USA

Colon carcinoma is a major cause of cancer related mortality. Colon cancer screening is effective; however, most screening strategies have not been validated by randomized controlled trials. Since the natural history of colon cancer is well understood, the screening situation can be simulated and screening strategies tested in silico.

Here we introduce a new microsimulation model, describing the natural history of colon carcinoma. Our model incorporates age dependent polyp appearance and progression rates as well as a patient specific individual polyp risk. Using these variables we can accurately model polyp and carcinoma distribution within a population as well as the number of individual polyps of a given patient. Our model thus offers the chance to test and compare various colon cancer screening strategies.
A novel mouse model of orthotopic metastatic colon cancer

O. Movadat, A. Wlodarski*, N. Wittkopf, M.F. Neurath, C. Becker
Department of Medicine 1, University of Erlangen-Nuremberg, Germany
*Institute of Immunology, Mainz, Germany

Introduction: Mouse models of colorectal cancer are important tools for examination of tumors and for investigation of new therapeutic chemicals. Currently extensive research not only on treatment, but also on chemoprevention of colon cancer is in progress. In order to conduct studies with physiological relevance, suitable animal models are required.

Methods: Mice were injected in the submucosal layer of the colonic wall with different human colon adenocarcinoma cell lines using the working channel of a mouse endoscopy system and an injection needle.

Results: Mice injected with tumor cells developed tumors in the colon. Tumor size, evaluated by weekly endoscopy, ranged from just detectable at day 7 to covering up to half of the colonic circumference on day 35. Histological examinations demonstrated poorly differentiated adenocarcinomas. Similar to human patients, in 39% of tested mice, metastases in lung and liver were detected. Chemotherapeutic agent 5-Floururacil was injected under endoscopic control, directly into colonic tumors as local therapeutic approach. To monitor success of therapy, tissue samples were examined for active Caspase 3. A significant higher activity in caspase 3 was seen in the 5-FU group.

Discussion/Conclusion: Here we demonstrate a novel murine model of colon cancer as the first model using human colorectal cancer cells injected submucosally in the colonic wall without surgery, by using a mouse colonoscopy.
Immunohistochemical screening of hMLH1 and hMSH2 gene mutations in patients diagnosed with colorectal cancer and microsatellite instability suspicion

F. Muresan¹, R. Simescu¹, I. Domşa², R. Buiga³, M. Cazacu¹
¹IVth Surgical Clinic, „Iuliu Haţieganu” University of Medicine and Pharmacy, Cluj-Napoca, România
²Department of Pathology, CF Clinical Hospital, Cluj-Napoca, România
³S.C. Santomar Oncodiagnostic S.R.L, Cluj-Napoca, România

Introduction: The aim of this study is the immunohistochemical screening of hMLH1 and hMSH2 gene mutations in patients diagnosed with colorectal cancers, suspected of having microsatellite instability, as diagnosed between January 2002 and December 2009 in the Surgery Department of the CF Clinical Hospital Cluj-Napoca (prospective non-randomized study).

Methods: Inclusion criteria were adenocarcinoma pathology finding and also minimum one of the revised Bethesda criteria for genetic testing of microsatellite instability in colorectal cancers. 110 eligible patients were divided in 2 study groups according to the number of Bethesda criteria met (group A – 1 criteria; group B – 2 or more criteria). Both groups were statistically compared considering the clinical and pathological parameters specific to the Lynch syndrome. We performed immunohistochemical staining to determine the expression of hMLH1 and hMSH2 genes in the tumors of all the patients.

Results: We found the differences in age, colorectal family history and right colon tumor site between the two groups to be statistically significant. Immunohistochemical stainings showed lack of hMLH1 gene expression in 9 patients and of hMSH2 gene in 4 patients respectively. In the group A, tumor of one patient showed lack of hMLH1 gene expression. In the B group, tumors of 8 patients showed lack of hMLH1 gene expression and tumors of other 4 patients showed lack of hMSH2 gene expression.

Discussion/Conclusion: Immunohistochemical staining can identify patients who need to be genetically tested for mutations of the DNA mismatch repair genes, in order to establish the correct diagnostic of Lynch syndrome.
Epiregulin promotes growth of colitis-associated tumors

Clemens Neufert, Christoph Becker, Maximilian Waldner, Ingo Backert, Markus F. Neurath
Medical Clinic 1, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany

Introduction: Colitis associated cancer (CAC) is a severe long-term complication of inflammatory bowel diseases such as Ulcerative colitis or Crohn’s disease. CAC exhibit a particular diagnostic challenge as it often grows flat and develops more rapidly than sporadic colorectal cancer (CRC).

Methods: Molecular mechanisms giving specifically rise to CAC have been poorly understood. To screen for potential factors that might influence initiation and growth of CAC, we have profiled gene expression patterns of such tumors in experimental models. The development of CAC and sporadic CRC was studied by the murine models AOM/DSS and APCmin, respectively. Comparative whole genome expression analysis for both tumor entities and control tissue was performed with high density microarrays. Evaluation of potential functional targets, included in vivo experiments with gene modified mice and application of recombinant proteins. In longitudinal studies, tumor development over time was monitored by mini-endoscopy.

Results: We could identify a set of genes which is differentially expressed between both colorectal tumor entities. Interestingly, Epiregulin (Ereg) was highly elevated and differentially expressed in CAC, but not in sporadic CRC. Strikingly, Ereg deficient mice are highly protected from colitis associated tumorigenesis which is particular remarkable as Ereg k.o. mice are more prone to colitis than matching wildtype animals. Further work showed that the addition of Ereg can promote tumor development in vitro and in vivo. And data from longitudinal mini-endoscopic studies with Ereg k.o. mice suggest that Ereg rather increases tumor growth than the initiation of CAC. By taking advantage of Ereg-reporter mice we could show that Ereg is produced by tumor stromal cells in CAC, providing evidence that Ereg might play a role in the stromal-epithelial crosstalk.

Discussion/Conclusion: Thus, our work suggests Ereg as a novel key player for the pathogenesis of CAC, and thus interference with Ereg production and/or Ereg signalling might serve as a potential therapeutic option for CAC.
Prediction of prognosis is not improved by the 7th edition of the TNM classification for colorectal cancer

Ulrich Nitsche, M.D. 1, Matthias Maak, M.D. 1, Tibor Schuster, Ph.D. 2, Beat Künzli, M.D. 3, Rupert Langer, M.D. 4, Julia Slotta-Huspenina, M.D. 4, Franz G. Bader, M.D. 1, Klaus-Peter Janssen, Ph.D. 1, Helmut Friess, M.D. 1, Robert Rosenberg, M.D. 1

1 Department of Surgery, Klinikum rechts der Isar, Technische Universität München, Munich, Germany, 2 Institute of Statistics and Epidemiology, Klinikum rechts der Isar, Technische Universität München, Munich, Germany, 3 Department of Surgery, Kantonsspital Liestal, Liestal, Switzerland, 4 Institute of Pathology, Technische Universität München, Munich, Germany

Introduction: The more complex seventh TNM edition replaced the sixth in 2009 with the aim of providing more precise prediction of prognosis. The prognostic value for colorectal cancer was compared for both editions of the TNM classification, and for an additional prognostic model.

Methods: Clinical and histopathological data of 2229 patients with colorectal cancer who underwent tumor resection between 1990 and 2006 were analyzed and compared using the sixth and seventh edition of the TNM classification and a further statistically model based on clinical and histopathological factors.

Results: With the sixth edition, 5-year survival was 96% for stage I, 90% for IIa, 86% for IIb, 90% for IIIa, 72% for IIIb, 48% for IIIc and 13% for IV. With the seventh edition, 5-year survival was 96% for stage I, 90% for IIa, 84% for IIb, 87% for IIc, 89% for IIIa, 72% for IIIb, 36% for IIIC, 15% for IVA and 10% for IVB. The stage shifted for only 155 patients (7%): from IIb to IIc (2%), from IIIb to IIIC (1%), and from IIIC to IIIB/A (4%). The performance of the seventh edition (c-index 0.83, 95% CI: 0.82–0.85) revealed no relevant improvement compared to the sixth edition (c-index 0.83, 95% CI: 0.82–0.84), or compared to a model based on independent prognostic factors (c-index 0.84, 95% CI: 0.83–0.86).

Discussion/Conclusion: The seventh TNM edition resulted in a more complex classification for daily clinical use, however, it does not provide greater accuracy in predicting colorectal cancer patients’ prognosis.
Integrative marker analysis and risk assessment in stage II colon cancer

Ulrich Nitsche, M.D.\textsuperscript{1}, Alexander Balmert\textsuperscript{1}, Tibor Schuster, Ph.D.\textsuperscript{2}, Franz G. Bader, M.D.\textsuperscript{1}, Helmut Friess, M.D.\textsuperscript{1}, Robert Rosenberg, M.D.\textsuperscript{1}, Klaus-Peter Janssen, Ph.D.\textsuperscript{1}

\textsuperscript{1}Department of Surgery, Klinikum rechts der Isar, Technische Universität München, Munich, Germany, \textsuperscript{2}Institute of Statistics and Epidemiology, Klinikum rechts der Isar, Technische Universität München, Munich, Germany

\textbf{Introduction}: Risk assessment for stage II colon cancer patients is groundbreaking for further therapeutic regimes but not reliable based on clinical parameters. The recurrence risk is in part defined by individual tumor genetics. We analyzed the value of a panel of molecular genetic markers for risk prediction.

\textbf{Methods}: 232 patients with colon cancer (T3–4 N0 M0) underwent complete resection of their primary tumor between 1987 and 2006, with a median follow-up of 97 months. Tissue was analyzed regarding microsatellite, KRAS and BRAF status. For 179 patients, gene expression levels of OPN, SASH1 and MACC1 were determined. The results were correlated with the individual risk of metachronous distant metastases. Allocation of patient into groups regarding their tumors' molecular signature was performed by two step cluster analysis.

\textbf{Results}: Mutations of KRAS occurred in 30\%, of BRAF in 15\% and microsatellite instability in 26\%. The risk of metachronous metastasis was associated with KRAS mutation (\(p = 0.033\)), microsatellite stable tumors (\(p = 0.015\)), and expression level of SASH1 (\(p = 0.049\)) and MACC1 (\(p < 0.001\)). On multivariable analysis, MACC1 remained the only independent parameter for prediction of recurrence risk (\(p < 0.001\)). Cluster analysis revealed four biological different groups of tumors. Patients with KRAS mutation, BRAF wildtype, microsatellite stable tumors and high MACC1 expression levels had the highest recurrence risk (16\%, 7 out of 43), whereas BRAF wildtype, microsatellite stable and low MACC1 expressing tumors had the lowest (4\%, 1 out of 26).

\textbf{Discussion/Conclusion}: Molecular characterization allows identifying different risk groups within the clinical similar cohort of stage II colon cancer patients. Of the here analyzed markers, MACC1 predicted the recurrence risk most accurately.
Surgical site infection in diabetic patients after colorectal surgery

1st Propedeutic Surgical Department, A.H.E.P.A. University Hospital, Aristotle’s University of Thessaloniki, Greece

Introduction: Surgical Site Infection (SSI) has a negative effect on wound healing, increases morbidity, mortality and Length of Hospital Stay. Diabetes mellitus (DM) is considered to be an independent risk factor for surgical infections. The purpose of the present study was to investigate the possible risk factors for SSI in colorectal surgery in correlation with postoperative glucose levels, in diabetic patients.

Methods: In this cohort study, a retrospective analysis of 1100 patients who underwent colorectal surgery between 1995 and 2010 was reviewed. Data were collected from patient’s medical records, discharge documents and the external office’s registry book.

Results: The cohort consisted of 185 patients under medication for DM. Surgical site infection was developed in 30 patients (16%) in whom blood glucose levels were found to be statistical significant elevated in the first 24 h (> 220 mg/dl, p = 0.03) and 48 h (> 190 mg/dl, p = 0.001), postoperatively. Body mass index, stomas and presence of drains was not found to be statistically significant risk factors for SSI.

Discussion/Conclusion: Postoperative elevated blood glucose levels were associated with increased surgical site infection. A strict postoperative glycemic control is advisable. Well designed randomized control trials are necessary in order to validate the association of glycemic control and surgical site infection in colorectal surgery.
Results of salvage abdominoperineal resection after failed chemoradiation therapy for epidermoid anal canal carcinoma: Retrospective analysis at a single institution

Ioannis Papaconstantinou, Anneza Yiallourou, Theodosios Theodosopoulos, Lazaros Samanides, Vassilis Smyrniotis, Alexios Fotopoulos, George Polymeneas, Constantinos Gennatas, Dionysios Voros
2nd Department of Surgery, Aretaieion Hospital, University of Athens, Greece

Introduction: The standard approach to anal canal cancer consists of combined radiation and chemotherapy. Although, disease control has been reported to have excellent results, as many as 40% of patients would develop locoregional disease progression. The treatment of choice for patients with persistent or recurrent disease is salvage abdominoperineal resection (APR). The purpose of this study is to review our experience with salvage surgery in this group of patients.

Methods: Medical records of all patients with anal canal cancer treated from 1997 to 2010 in our department were retrospectively reviewed. Nine patients who presented with persistent or locally recurrent anal canal cancer received salvage surgery. Before surgery, all of the patients had received chemoradiation therapy.

Results: There were 9 patients (7 women, 2 men) with a mean age of 61 years (range 50–79). Six patients underwent radical salvage surgery for persistent disease and 3 patients for recurrent disease. There were no deaths attributable to operation. The median follow-up time was 24 (range 2–60) months after salvage surgery. Two patients died of disease progression, with a median survival time of 24 (range 12–36) months. At the time of last follow-up, six patients were alive without evidence of recurrent disease, and one patient was lost to follow-up. The median follow-up time for survivors was 23 months (range 2–60).

Discussion/Conclusion: Long-term survival can be achieved in the majority of patients who undergo radical salvage abdominoperineal resection after failed chemoradiation therapy for epidermoid carcinoma of the anal canal.
Gastrointestinal quality of life after laparoscopic-assisted sigmoidectomy for diverticular disease

Itai Pasternak, M.D.¹, Nicole Wiedemann, M.D.², Giacinto Basilicata, M.D.³, Gian A. Melcher, M.D., F.A.C.S ¹
¹Department of Surgery, Uster Hospital, 8610 Uster, Switzerland
²Department of Gynecology, Uster Hospital, 8610 Uster, Switzerland
³Department of Surgery, Liestal Hospital, 4410 Liestal, Switzerland

Introduction: Laparoscopic-assisted sigmoidectomy is a widely applied technique in the operative treatment of diverticular disease. Treatment guidelines recommend operation of complicated diverticulitis and after recurrent attacks of uncomplicated diverticulitis. These guidelines have become subject to controversy. The objective of this study was to assess disease-related quality of life after laparoscopic sigmoidectomy.

Methods: Data were collected retrospectively. Patients filled in a form describing their quality of life. All patients undergoing elective operation for diverticular disease between 1999 and 2006 at the Department of Surgery of the Uster Hospital, a regional medical center in Switzerland were included. The measurement tool we used is the Gastrointestinal Quality of Life Index. Paired or unpaired t-tests were applied to determine statistical significance of differences observed.

Results: 130 patients were included and 120 questionnaires were available for analysis. Mean follow-up was 40 months. 48% reported a Gastrointestinal Quality of Life Index > 100 before the operation rising to 83% after the operation (p < 0.0001). Mean Gastrointestinal Quality of Life Index was 95 before and 114 after the operation (p < 0.0001). Female patients reported lower Gastrointestinal Quality of Life Index rates. Younger patients were at greater risk for recurrent symptoms. Overall, 96% were satisfied with the operation.

Discussion/Conclusion: The results in this study population show that in a majority of patients who underwent elective laparoscopic-assisted sigmoidectomy for recurrent diverticulitis gastrointestinal quality of life improved with the operation.
Effect of preoperative radiochemotherapy on lymph node retrieval after resection of rectal cancer

Henrikas Pauzas, Tadas Latkauskas, Paulius Lizdenis, Zilvinas Saladzinskas, Algimantas Tamelis, Dainius Pavalkis
Lithuanian University of Health Sciences, Kaunas, Lithuania

Introduction: This study assesses the role of preoperative radiochemotherapy on the number of lymph nodes detected in the tumor-bearing specimen.

Methods: Retrospective data of 138 patients who underwent surgery for stage II and III rectal cancer without preoperative radiochemotherapy during the period 2004–2006 (control group), compared with prospective data of 46 patients who received preoperative radiochemotherapy during the period 2007–2008 (study group).

Results: A positive lymph nodes were detected in 89 patients (64%) in the control group, comparing with 13 patients (28%) in the study group (p < 0.05).
A mean of 13.5 (SD 6.4) lymph nodes per specimen were detected in control patients, while a mean of 6.54 (SD 2.88) lymph nodes per specimen were detected in the study group patients (p < 0.05).
A mean of 5.12 (SD 6.4) lymph nodes per specimen were detected in control group, a mean of 2.15 (SD 0.09) lymph nodes per specimen were detected in the study group (p < 0.05).

Discussion/Conclusion: Preoperative radiochemotherapy for advanced rectal cancer significantly decreased the number of lymph nodes detected within the tumor-bearing specimen. This resulted also in significant decrease of metastatic lymph nodes detected in the specimen and fewer stage III (N+) patients diagnosed.
Microvessel density could be strong prognostic marker after radiotherapy in rectal cancer

D. Pavalkis¹, S. Svagzdys¹, V. Lesauskaite², Z. Saladzinskas¹, A. Tamelis¹
¹Clinic of Surgery, Academy of Medicine, Lithuanian University of Health Science,
²Institute of Cardiology, Academy of Medicine, Lithuanian University of Health Science, Kaunas, Lithuania

**Introduction:** The extent of angiogenesis is an important prognostic factor for colorectal carcinoma, however, there are few studies concerning changes in angiogenesis with radiotherapy (RTX). Our aim was to investigate changes in tumor angiogenesis influenced by radiotherapy to assess the prognostic value of the microvessel density (MVD) in overall survival after radiotherapy.

**Methods:** Tumor specimens were taken from 101 patients resected for rectal cancer. The patients were divided into three groups according to the treatment they received before surgery (not treated, a short course, or long course of RTX). Tumor specimens were paraffin-embedded and immunohistochemistry was performed with primary antibody against CD-34 to count MVD.

**Results:** MVD was significantly lower in the group of patients treated with a long course of RTX. We found a significant prognostic rate for MVD when the density cut off was near 130. When the MVD was lower than a cut off of 130, the survival period significantly increased. According the Cox regression model the mortality rate is significantly higher if the MVD is higher than 130, if the histological grade is moderate/poor, if the tumor is T3/T4, and if the patient is male adjusted by other variable in model.

**Discussion/Conclusion:** According our results a long course of radiotherapy significantly decreased angiogenesis in rectal cancer tissue. MVD was is a favorable marker for tumor behavior during RTX and a predictor of overall survival after this long course of RTX.
Gasless transanal endosurgery and transanal excision of rectal cancer: Experience from a single center in Moscow

I. Peresada, Y. Shelygin, S. Chernyshov
State Research Center of Coloproctology, Moscow, Russia

Introduction: Gasless transanal endoscopic surgery (GTES) allows to excise rectal tumors by means of conventional laparoscopic tools via operative rectoscope. Transanal excision (TE) by Parks also used for low rectal tumors. Evaluation of the effectiveness of GTES and TE for T_{is}-1N0M0G1–2 rectal carcinomas (< 3 cm) was the aim of the study.

Methods: Between 1999 and 2011, 114 patients (49 male) (mean age 62.5 [range 34–86]) with early rectal cancer underwent GTES (n = 94) and TE (n = 20). Mean size of lesions in GTES and TE groups was 2.7 ± 1.1 cm vs. 3.4 ± 1.5 cm (p = 0.0265), and mean distance from dentate line was 5.0 ± 2.6 cm vs. 1.9 ± 1.6 cm (p < 0.0001).

Results: No conversions to major surgery were needed. The median operating time and blood loss for GTES and TE groups were 58.9 ± 25.1 vs. 38.7 ± 16.4 minutes (p = 0.0003) and 42.5 ± 25.4 vs. 43.5 ± 34.2 ml (p = 0.2381) respectively. Postoperative morbidity and mortality rate in GTES and TE was following: 6/94 (6.4%) vs. 2/20 (10%); 1/94 (1.1%) vs. 0/20, consequently. Pathological examination revealed 18 – pT_{is}, 63 – pT1G1-3, 12 – pT2G1-2 and 1 – pT3G3 after GTES, and 6 – pT_{is}, 12 – pT1G1-3, 1 – pT2G1 and pT3G3 after TE. 11 patients with pT2–3 carcinomas had postoperative EBRT (45 Gy). At mean follow up of 30.2 ± 25.7 months (2–109), local recurrence developed in 2 (3.5%) patients after GTES (pT1G2). One of them was salvaged by APE and died from cardiovascular diseases 31 months after second operation, another 86-old man refused from further treatment and died within 4 months due to progressive disease.

Conclusion: GTES and TE are safe, effective and simple surgical procedures for patient with early rectal carcinomas.
Anal sphincter preservation in ultra low rectal cancer surgery – Suffering for the patient or chance to continue customary life?

D. Pikunov, E. Rybakov
State Research Center of Coloproctology, Moscow, Russia

Introduction: Last decade the question of quality of life after surgery for very low rectal cancer is being discussed widely, especially focusing whenever preserve anal sphincters or not.

Methods: Since 2005 sixty (31 male) patients with median age 54 (range 29–71) were operated for rectal cancer T2–3 within 1 cm from the dental line with partial anal sphincter preservation. Thirty-two patients received prolonged course of preop chemo-radiotherapy. Anorectal reconstruction with smooth muscle plasty and C-shaped colonic pouch was used in total number of procedures. All the patients were temporary defunctioned. Protective stomas were closed at 8–25 weeks after the primary surgery. Fourteen patients received a course of biofeedback (BFB) therapy before stoma closure. 42 patients were followed up more than 24 months after stoma closure. We used FIQL, SF-36 questionnaire before and 3, 6, 12, 24 months after stoma reversal as well as myography, vectrum volumetry and anal manometry at the same times.

Results: After a median follow-up of 38 months, local recurrence was determined in three (5%) cases. Gradual improvement of continence had being registered during 12 months after stoma closure and BFB-therapy made for earlier adaptation. We registered almost equal SF-36 (both Mental/Physical Components) results before stoma closure and 3 months later (44.2/38.1 and 45.4/36.8 respectively). With the course of time Mental Component was being improved faster then Physical one, and by 24 months after stoma closure they were 54.6 and 44.2 respectively.

Discussion/Conclusion: Acceptable oncological and functional outcome of suggested surgery seems to be an attractive alternative to APR with permanent stoma for high-motivated patients.
Adrenal metastases of colorectal carcinomas

Dr. J. Christian Pitt, Dr. K. Peitgen
Department of General and Visceral Surgery, Knappschaftskrankenhaus Bottrop, Osterfelder Str. 157, 46242 Bottrop, Germany

Introduction: Metastases of colorectal carcinoma (CRC) usually involve the liver and, less frequently, the lungs. The adrenal glands are seldom involved, particularly as the only site of spread. A standard therapy recommendation does not exist.

Methods: Files of patients treated for CRC in our hospital from 2006 were retrospectively evaluated.

Results: Solitary adrenal metastases were found in three patients. All primary tumors were located in the rectum:
One patient presented with rectal cancer and a synchronous 5 cm adrenal mass. Conventional adrenalectomy confirmed metastasis of rectal cancer. He underwent rectum resection. Hepatic, peritoneal and retroperitoneal tumor spread occurred beginning three months postoperatively. He succumbed 33 months after adrenalectomy.
One patient underwent radiofrequency ablation of a solitary adrenal metastasis. He had undergone rectum resection 7 years, liver resections 7 and 5 years, and lung resection 2 years before. We performed open adrenalectomy because of tumor growth 6 months later, and he was alive with disease 5 years later.
One patient showed a solitary adrenal metastasis 5 months after abdominoperineal resection. She underwent retroperitoneoscopic adrenalectomy. 13 months later, liver metastases developed.

Discussion/Conclusion: According to the limited data in the literature, adrenal CRC metastases usually stem from rectal primaries. The risk for further metastases is high. Both is in good agreement with our data. As and when adrenalectomy can be performed with low morbidity, ideally by a minimally invasive approach, we consider it the therapy of choice to achieve local tumor control and possible cure.
Lymph node yield after rectal resection in patients treated with neoadjuvant radiation: A systematic review and meta-analysis

Sebastian Pohle\(^1\), Philipp Quentmeier\(^2\), Martin Loos\(^2\), Ulrich Nitsche\(^2\), Matthias Maak\(^2\), Tibor Schuster\(^3\), Rupert Langer\(^4\), Helmut Friess\(^2\), Thomas Kocher\(^1\), Robert Rosenberg\(^1,2\)

\(^1\)Department of Surgery, Kantonsspital Baden, Switzerland; \(^2\)Department of Surgery, Klinikum rechts der Isar, Technische Universität München, Munich, Germany; \(^3\)Institute of Statistics and Epidemiology, Klinikum rechts der Isar, Technische Universität München, Munich, Germany; \(^4\)Institute of Pathology, Technische Universität München, Munich, Germany

Introduction: The total number of resected lymph nodes has a high prognostic impact in colorectal cancer patients. In rectal cancer patients, lymph node numbers appear to be lower in patients after preoperative radiation compared to patients without preoperative radiation and the same surgical quality. A meta-analysis was performed to assess the impact of preoperative radiation on the number of total resected lymph nodes and the number of tumor-infiltrated lymph nodes.

Methods: We searched the databases of PubMed, Medline, Embase, Cochrane Library, and Ovid for studies published between 1990 and 2011 that compared lymph node numbers in rectal cancer specimen after preoperative radiation and without preoperative radiation. 19 studies, which were selected from 1221 identified studies, met our search criteria and were assessed. In total, data from 24,510 patients were evaluated. Twelve studies evaluated the lymph node numbers after preoperative radiochemotherapy (RCTX), five studies after preoperative radiotherapy (RTX) and two studies after preoperative RCTX or RTX. All studies used TME as surgical standard. Random and fixed-effects meta-analytic models were used where indicated, and between-study heterogeneity was assessed. End-points included total numbers of resected lymph nodes and total number of tumor-infiltrated lymph nodes.

Results: The 9021 patients after preoperative radiation had in average 3.52 lymph nodes less in the specimen compared to the 15,489 patients after primary surgery (95% CI: -3.04; -5.14) \((Z = 7.66; p < 0.0001)\). While preoperative long-term radiochemotherapy (RCTX) revealed 4.09 lymph nodes less in the specimen compared to primary surgery (95% CI: -3.04; -5.14) \((Z = 7.66; p < 0.0001)\), a preoperative short-term radiotherapy (RTX) was associated with 1.66 lymph nodes less compared to primary surgery (95% CI: -0.92; -2.39) \((Z = 4.44; p < 0.0001)\). The number tumor-infiltrated lymph nodes was in average 0.55 lower (95% CI: 0.21; -1.31) after preoperative radiation \((n = 1496 patients)\) compared to the 2150 primary resected patients and did not differ significantly \((Z = 1.41; p = 0.16)\).

Discussion/Conclusion: The total number of resected lymph nodes is significantly lower after preoperative radiation in rectal cancer patients. In contrast, the number of tumor infiltrated lymph nodes does not seem to be influenced by preoperative radiation. Therefore, the total number of lymph nodes reflects a therapy effect and does not represent a quality criterion in rectal cancer surgery after preoperative radiation.
Preoperative chemoradiotherapy increases sphincter-sparing procedure rate for rectal carcinoma patients

A. Rasulov\textsuperscript{1}, Y. Sheligin\textsuperscript{1}, S. Zhdankina\textsuperscript{1}, A. Boiko\textsuperscript{2}, I. Drosheeva\textsuperscript{2}

State Research Center of Coloproctology, Moscow, Russia\textsuperscript{1}
Moscow Herzen Research Oncology Institute, Moscow, Russia\textsuperscript{2}

Tumor shrinkage influencing by preoperative chemoradiotherapy (CRT) might result in sphincter preservation for low rectal carcinoma (LRC).

**Material and methods:** From 2006, 321 patients with T3–4N0–2 or T2N0–2 rectal carcinoma located close to an anus, enrolled into study. Of these patients, 176 received preoperative CRT and 145 undergone surgery alone. Average distance from anal verge to tumor was 5.0 ± 2.3 and 6.8 ± 2.8 cm, with 3.8 ± 1.2 (n = 115) and 4.2 ± 1.5 cm (n = 64) for LRC in CRT and surgery group, respectively.

First 5 days patients were given IVB 5-FU 350 mg/m\textsuperscript{2}, next 3 days – cisplatin 30 mg per dose, concurrently with external beam radiation 4 Gy and then 2.5 Gy/day in 2 fractions up to total dose 47 Gy. Timing surgery was 5–7 weeks after CRT. Patients were given adjuvant Xelox.

**Results:** Tumor downstaging revealed in 66.4% of irradiated patients. Complete and near complete tumor regression registered in 35.4% (11.4% and 24%, respectively). Distance from anal verge to tumor increased up to 5.7 ± 2.1 cm with 4.4 ± 1.1 cm for LRC.

There was increase of sphincter-sparing procedures (SSP) rate (72.2% vs. 44.8%, p < 0.05) including partial sphincter resection (19.1% vs. 5.2%, p < 0.05) after CRT comparing to surgery. Postoperative complications developed in 27.6% irradiated patients and 20.1% after surgery (p > 0.05). With follow-up 4–60 months local recurrences developed in 1.3% and 9.7% (p = 0.02), metastases – in 10.1% and 7.9% (p > 0.05) with DFS – 82.1% and 79.1% in CRT and surgery (p > 0.05).

**Conclusion:** Preoperative CRT results in increase of SSP rate for low rectal carcinoma with good local control.
HLA class I expression in colorectal cancer; prognostic and predictive relevance

M.S. Reimers, M.D., E.C.M. Zeestraten, M.D., S. Saadatmand, M.D., G.J. Liefers, M.D., Ph.D., Prof. C.J.H. van de Velde, M.D., Ph.D., P.J.K. Kuppen, Ph.D.

aDepartment of Surgery, Leiden University Medical Center, Leiden, The Netherlands

*Both authors contributed equally to this work

Introduction: Down regulation of HLA Class I is an import mechanism by which tumors avoid immune surveillance. The goal of this study was to validate the prognostic value of HLA Class I expression in colorectal cancer.

Methods: 416 colorectal cancer patients treated with surgery for their primary tumor in the LUMC between 1991 and 2001 were included. Tumor tissue sections were immuno-histochemically stained for HCA2 and HC10, based on which HLA Class I expression could be determined.

Results: HLA Class I loss of expression showed, although not related to disease stage, a significantly better Overall Survival and Disease Free Survival (p value 0.04 and 0.013) compared to patients with partial or expression of HLA class I. In multivariate analysis HLA Class I expression status remained borderline significant for OS (p-value 0.053) but was not an independent, significant predictor for DFS.

Discussion/Conclusion: HLA Class I expression status is a prognostic marker in CRC, but seems not related to disease progression. Currently, we are studying additional parameters, like the presence of regulatory T cells, which have additional prognostic value to tumor expression of HLA.
Groin metastases of anal carcinoma: Surgery or chemoradiation

E.G. Rybakov, S.V. Chernyshov
State Research Center of Coloproctology, Moscow, Russia

Introduction: Locoregional dissemination is common for anal carcinoma (AC). While multimodality treatment, i.e. chemoradiation (CRT) is a standard treatment for primary AC, in cases of groin lymphadenopathy both inguinal lymphadenectomy (ILAE) or CRT are possible. The aim of prospective study was to compare treatment outcomes after ILAE or CRT.

Methods: 151 patients (mean age 58 ± 10.8, 25-male) with AC were treated from 1996–2010. Synchronous metastases of AC to the inguinal lymph nodes were detected in 15 (10.0%) patients, metachronous – 6 (4.0%). Both LAE (n = 8) or CRT (n = 13) were used for treatment.

Results: RT at a dose of 55–70 Gy resulted complete regression of metastases in 9 patients with synchronous inguinal metastases (5 patients had no evidence of disease from 2 to 7). There was incomplete regression in 4 patients after CRT. Both patients with metachronous inguinal metastases had successful CRT. ILAE was used in 8 patients (4 synchronous and 4 metachronous). Mean time of operation – 65 (50–74) min. Of them 4 patients had postoperative wound break and 3 patients had non-clostridial infection. All patients after operation had prolonged (up to 8 weeks) lymphorrhea. ILAE provide locoregional control of metastases in 6 patients. Two patients had regional recurrence. Of them one was successfully treated by RT. The 5-year survival rate of patients with cancer of the anal canal with synchronous and metachronous metastasis was 45.9%.

Conclusion: Management of inguinal lymph nodes metastases of AC should be individualized as both CRC or ILAE provides similar oncologic effectiveness but associated with different types of complications.
Primary mixed goblet cell carcinoid/-adenocarcinoma of the cecum with stenotic metastasis in the sigmoid presents as a rare cause of a decompensated colon ileus with sigmoid stenosis

A. Sahin¹, S. Tschuppert¹, A. Wodzynski², M. Trippel², S. Saravanja³, A. Keerl¹, R. Rosenberg¹, T. Kocher¹

¹Department of Surgery, ²Institute for Pathology, ³Institute for Radiology, Kantonsspital Baden, Switzerland

Introduction: Primary mixed goblet cell carcinoid/-signet cell adenocarcinoma of the cecum is a rare entity and has often a limited prognosis. Only case reports are to be found in the literature.

Methods: A case report with review of the literature was performed.

Results: We would like to present the case of a 78-year-old male with a rare cause of a sigmoid stenosis with severe colonic obstruction. The Patient suffered from abdominal pain and meteorism over the last 6 years. A colonoscopy in 2005 revealed a sigmoid diverticulosis. In 2011, colonoscopy detected a sigmoid stenosis due to sigmoid diverticulitis. The examination was limited to the left flexure. CT scan showed a sigmoid stenosis with a 7 cm extended colon and an unclear mass in the cecum/appendix. Laparotomy, decompression of the colon, right colectomy and anterior resection with radical lymphadenectomy and protective loop ileostomy was performed. Intraoperative fresh frozen section revealed a sigmoid metastasis of a signet cell carcinoma of the cecum and no other distant metastases or peritoneal carcinomatosis were evident. Histopathological evaluation revealed a pT4a, pN2b (7/45), pM1b (LYM (8/24), PER, OTH), R0, G3, L1, V1, Pn1) primary mixed goblet cell carcinoid/-signet cell adenocarcinoma of the cecum with a high number of lymph node metastases, distant metastases to the sigmoid, regional peritoneal carcinomatosis of the omentum and no evidence of microsatellite instability. Our interdisciplinary tumor board recommended short follow-up controls. A systemic chemotherapy should be performed after detection of tumor recurrence, this due to the age of the patient, the aggressive course of disease and the limited response to chemotherapy.

Discussion/Conclusion: Goblet cell carcinoid is a clinicopathologically rare tumor that typically manifests itself in the appendix/cecum and metastasizes frequently. The extended number of lymph node metastases, the regional evidence of peritoneal carcinomatosis in the omentum and the solitary sigmoid metastasis confirm the aggressive clinical course of the tumor entity.
Quality of life after sphincter-preserving rectal cancer resections

J. Scheele, M. Meier, D. Henne-Bruns, M. Kornmann
Department of General, Visceral, and Transplantation Surgery, University of Ulm, 89075 Ulm, Germany

Introduction: The need to perform an abdomino-perineal resection (APR) in rectal cancer (RC) is decreasing due to better surgical techniques and effective neoadjuvant treatment strategies resulting in down-sizing/-staging. Presently, knowledge about quality of life (QL) of RC patients after sphincter-preserving anterior resection (AR) is still scarce.

Methods: Between 1998 and 2008 we identified 293 RC patients receiving an AR and 201 right-sited colon cancer (CC) patients receiving an oncologic colon resection as first control group (control surgery). Healthy lay persons of the same age were used as second control group (control no surgery). Patients and lays were requested to answer the standardized EORTC QL questionairs QLQ-C 30 and -CR38. Additionally, the estimated stool frequency per day should be stated.

Results: One hundred sixteen QL questionairs from RC patients, 105 from CC patients, and 103 from lay persons were evaluable. The global health status did not differ between the groups. Regarding symptoms defecation problems and diarrhea were, as expected, more frequent in RC patients. The median stool frequency was 3 (range: 1–25), 2 (range: 1–12), and 1 (range: 0–3) for RC, CC, and lay persons, respectively. Role functioning (RF2), future perspectives (FU), and financial difficulties (FI) tended to poorer scores in the cancer groups, especially in CC, in comparison to lay persons. Interestingly, physical functioning (PF2) was regarded better for RC and CC patients compared to lay persons.

Discussion/Conclusion: Despite clear long-term symptoms (defecation problems and diarrhea) associated with AR after rectal cancer resection the overall health status did not differ from controls. The knowledge of surviving cancer may even be associated with a better physical functioning.
Postoperative complications and risk factors in robotic surgery for rectal cancer

O. Sgarbura, M. Eftimie, V. Tomulescu, I. Popescu
Fundeni Institute of Digestive Diseases and Liver Transplantation, Bucharest, Romania
University of Medicine and Pharmacy, Bucharest, Romania

Introduction: Robotic surgery has come in the spotlight in the last six years with the promise of a more precise dissection and suturing under a better view and with better ergonomics. That is why it was rapidly adopted in colorectal surgery even if we are still waiting for the high level evidence concerning laparoscopic rectal resections for cancer. Today, when larger series are available, a complication and risk factor analysis may enhance the understanding of this procedure.

Material and methods: Consecutive patients undergoing elective robotic rectal surgery for cancer from the startup of the robotic programme at the Fundeni Clinical Institute on the 1 January 2008 until 1 March 2011 were included in the study group. Information about the 53 patients was retrieved from a prospectively collected database.

Results: The interventions were performed for rectal adenocarcinoma and included low and ultra-low anterior resections and abdominoperineal resections. The overall complication rate was 20%. The most common complication was anastomotic leakage (8%), followed by ileus/obstruction, intrapelvic abscess, and wound infection. Overall reintervention rate was 10% (hemoperitoneum, ileus/obstruction, anastomotic leakage). Major risk factor was preoperative radiochemotherapy (p < 0.05). Other risk factors were diabetes mellitus and infraperitoneal tumor location.

Conclusions: Risk factors and complications acknowledgement can contribute to a better patient selection and a more adequate postoperative management for robotic surgery improving the results of this emerging technique.
Screening of irregular bowel movement frequency as functional risk factor of colorectal cancer

Constantine Shemerovskii
Institute of Experimental Medicine, St. Petersburg, Russia

Introduction: Bowel habit according to chronobiology is one of the basic circadian rhythm with normal frequency not less than 7 times per week. Stool frequency according to Rom-III criterions of constipation is less than 3 times per week. Screening of irregular bowel habit (between 3 and 7 times per week) may be useful because low bowel movement frequency is risk factor for colorectal cancer (1, 2).

Aim and methods: Aim of this study was to compare the circadian bowel movement frequency in persons with regular and irregular bowel habit. Valid self-report questionnaires (1 page – 18 questions) was used in 100 participants of UEGW in Barcelona (41 female, 59 male, 30–64 yr). Chronophysiologic approach was used to determine frequency and acrophase (the most frequent moment in 24 hour period) of the circadian rectal rhythm. Rhythm with frequency 7 times per week means regular bowel rhythm (RBR). Stool frequency from 1 to 6 per week means irregular bowel rhythm (IBR).

Results: RBR had 57 persons, IBR was diagnosed in 43 persons. There were 18 women + 39 men with RBR and 23 women + 20 men with IBR. IBR of I stage (5–6 stools per week) was diagnosed in 92% of persons, II stage (3–4 per week) – in 6%, III stage (1–2 per week) – in 2%. RBR was link predominantly (91%) with morning stool acrophase. IBR was link mainly (88%) with absence of morning stool. Shift of morning stool acrophase from the optimal period (before 12:00 h) to the pessimal one (from 12:00 to 24:00 h) in persons with IBR was diagnosed almost 10 times more often than in persons with RBR. The impact of stool acrophase shift (58%) in IBR was higher, than impact of sleep irregularity (17%), low physical activity (13%) and underfeeding (12%). Laxative used 6% of persons with RBR, but 23% of persons with IBR. Persons with RBR have Quality of life 15% higher than persons with IBR.

Conclusion: 43% of investigated European gastroenterologists are patients with IBR, which used laxatives 4 times more frequently than persons with RBR. Patients with IBR have 15% lower quality of life. The shift of stool acrophase is the most significant risk factor for IBR. Absence of morning stool increases risk of IBR almost 10 times. Screening of IBR may be useful for earlier prevention of colorectal cancer, because constipation (a bowel movement frequency of less than daily) increases risk of colorectal cancer more than 2 times (1, 2).

References:


Specific activity of cyclin-dependent kinase 1 predicts the recurrence of stage II colon cancer

Masaki Shibayama\(^1\), Eliane C.M. Zeestraten\(^2\), Matthias Maak\(^3\), Tibor Schuster\(^4\), Ulrich Nitsche\(^3\), Tomoko Matsushima\(^1\), Satoshi Nakayama\(^1\), Keigo Gohda\(^1\), Hirokazu Kurata\(^1\), Helmut Friess\(^3\), Cornelis J.H. van de Velde\(^2\), Hideki Ishihara\(^1\), Robert Rosenberg\(^3\), Peter J.K. Kuppen\(^2\), and Klaus-Peter Janssen\(^3\)

\(^1\)Sysmex Corporation, Central Research Laboratories, Kobe, 651-2271 Hyogo, Japan; \(^2\)Department of Surgery, Leiden University Medical Center, 2300 Leiden, The Netherlands; \(^3\)Chirurgische Klinik und Poliklinik, Klinikum rechts der Isar, Technische Universität München, 81675 Munich, Germany; \(^4\)Institut für Medizinische Statistik und Epidemiologie, Technische Universität München, 81675 Munich, Germany

Introduction: There are no established prognostic biomarkers for stage II colon cancer (CC). Therefore, we investigated whether the activity of cyclin dependent kinases (CDK), pivotal regulators of cell proliferation, predicts the recurrence of CC.

Methods: 254 patients with completely resected (R0) UICC stage II CC were analyzed retrospectively from two independent cohorts (Germany and the Netherlands). No patient received adjuvant chemotherapy. Development of distant metastasis was observed in 27 patients (median follow-up: 86 months). Protein expression and activity of CDKs were measured on fresh-frozen tumor samples.

Results: Specific activity of CDK1 (CDK1SA) significantly correlated with distant metastasis (concordance index = 0.69, 95% CI: 0.55–0.79, \(p = 0.036\)). Cut-off derivation by maximum log-rank statistics yielded a threshold of CDK1SA at 11 (unit, \(p = 0.029\)). Accordingly, 59% of patients were classified as the high-risk group (CDK1SA > 11). Cox proportional hazard analysis revealed that the CDK1SA is an independent prognostic variable (hazard ratio = 6.2, 95% CI: 1.44–26.9, \(p = 0.012\)). None of the currently accepted clinical risk factors (e.g., perforation, T4 stage or < 12 resected lymph nodes), nor the B-RAF mutation status successfully predicted recurrence. Moreover, CDK1 specific activity was not confounded by any of these factors. Interestingly, CKD1SA was significantly elevated in microsatellite stable tumors.

Discussion/Conclusion: Specific activity of CDK1 is a promising biomarker for the risk of metastasis in stage II colon cancer.
Colorectal cancer in the region with enormously high occurrence rate: The projection of screening program and clinical practice

Julius Spicak¹, Petr Stirand¹, Pavel Drastich¹, Tomas Hucl¹, Marek Benes¹, Pavel Wohl¹, David Kamenar³, Vladimír Nosek⁴, Ondrej Urban³, Miroslav Zavoral²
¹Department of Hepatogastroenterology, Institute for Clinical and Experimental Medicine, Prague; ²Department of Internal Medicine, Central Military Hospital, Prague; ³Department of Internal Medicine, Hospital in Vítkovice, Ostrava; ⁴Department of Gastroenterology, Hospital in Jablonec nad Nisou, Czech Republic

Introduction and objective: The national colorectal cancer screening programme in the Czech Republic is based on FOBT and colonoscopy. The number of colonoscopies has been constantly increasing, reaching approximately 200,000 per year in a population of 10.5 million. Although the overall incidence of colorectal cancer is high throughout Europe, regional figures differ considerably, with the Czech Republic occupying the leading position. Each region should, therefore, monitor and evaluate all the related aspects and adapt rules of management accordingly. The aim of our multicenter prospective study was to analyze issues of the quality of colonoscopy, the incidence of colonic neoplasias, and the projection of screening.

Results: A total of 2126 consecutive colonoscopies performed during 2009–2010 at four regional tertiary centres in people older than 40 years of age were analyzed. The occurrence rates of adenomas, advanced adenomas, and carcinomas in those < 45, 45–50, and > 50 years were 8.3%, 25.3%, and 48.3%; 3.3%, 10.0% and 31.3%; 1.1%, 2.0%, and 6.8% respectively. Only 59.9% of advanced neoplasias were potentially accessible by sigmoidoscopy. Colonoscopy was performed as a screening procedure in 320 males and 245 females; any between-gender differences were not statistically significant (p ≤ 0.05). A total of 931 (43.8%) patients reported a positive family history. The occurrence rates of advanced adenomas and carcinomas were 6.8% and 2.1%, respectively, figures significantly lower than in other patients (44.6% and 8.5%, respectively, p ≤ 0.001). The mean age in both groups was 47 and 63 years. In screening subgroup, 301 (53.3%) of the 565 patients reported a positive family history. The occurrence rates of advanced adenomas and cancers were 3.3% and 0.9%, significantly less than in people without a positive family history (27.6% and 4.9%, respectively). The mean age of these subgroups was 45 and 52 years. In 245 patients colonoscopy was done after positive FOBT, and in 320 as a primary screening method. The occurrence rate of advanced neoplasias after positive FOBT was significantly higher (21.2% vs. 13.1%, respectively p ≤ 0.01).

Conclusions: The rate of neoplasias detected by colonoscopy in the Czech Republic is extremely high even in those under the age of 50, and the screening rules should be adapted accordingly. The proportion of people with a positive family history is also high. The disproportionately low occurrence of neoplasias among them could be explained by their youth, suggesting they are well informed and seek screening early. The relatively young age of screened people indicates that the campaign should be focused more on those who are older.

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The effect of a nationwide screening program on the diagnosis of colorectal cancer (CRC) in a region with an enormously high occurrence

Julius Spicak¹, Marek Benes¹, Tomas Hucl¹, Petr Stirand¹, Pavel Drastich¹, Ondrej Urban², Vladimir Nosek³
¹IKEM, Prague, Czech Republic
²Teaching Hospital Ostrava-Vitkovice, Ostrava, Czech Republic
³Hospital Jablonec nad Nisou, Jablonec nad Nisou, Czech Republic

Introduction: The incidence of colorectal cancer (CRC) in the Czech Republic has exceeded 70/100,000 inhabitants per year. A nationwide screening program based on fecal occult blood testing (FOBT) and colonoscopy, combined with a centrally driven awareness-raising campaign were launched in 2000, reaching a considerable proportion of those eligible. The number of FOBT procedures and colonoscopies has increased during the last decade (currently more than 200,000 colonoscopies per year in a country with a population of 10 million, and a dense network of endoscopic facilities).

Aims, patients, methods: The aim of this prospective multicenter study was to determine how this program and campaign have projected into the diagnostic process of CRC in real-life patients. A total of 190 consecutive patients with CRC in different and remote regions were enrolled.

Results: There were 117 males and 73 females. The mean age of all patients was 67 years (SD 11.17). The interval between the first symptoms and the first time of seeing a physician did not exceed 3 months in 91.5% patients, and the diagnosis was concluded (the interval between the first presentation and diagnostic colonoscopy) within another 3 months in 85.8% patients. Altogether, 74 (39%) of all CRCs were detected by the screening process. In 51, FOBT preceded and, in 23 patients, a primary screening colonoscopy was performed. In 20 patients, the screening colonoscopy was done despite a negative FOBT. In 18 patients, definitive colonoscopy was preceded by colonoscopy with either a normal (5) or presumably non-malignant finding. The mean interval between the first and definitive colonoscopy was 44 (14–3684) days in these patients. A total of 128 (67.3%) patients were informed about the risk of CRC. Of this number, 55 were informed by TV and 49 by the physician.

Conclusions: In patients diagnosed to have CRC, their previous awareness of the risk of CRC did not exceed 70%. The screening program resulted in the detection of 39% of all cases of CRC. The intervals between the first symptoms, seeing a physician, and definitive colonoscopy are acceptably short and attest to the availability of endoscopic methods. While, in a not negligible minority, the first colonoscopy provided an incorrect finding, this did not slow the entire diagnostic process substantially. Despite regular visits, a relatively low proportion of patients were explicitly informed by a physician. A more aggressive and permanent campaign, and an emphasis on endoscopic quality issues, would further boost the efficacy of the nationwide screening program.
Surgical reoperations in cases of postoperative sepsis subsequent to the surgical treatment of colorectal cancer

G. Statescu¹, A. Statescu², M. Carausu²
¹Providenta Hospital Iasi, Iasi, Romania
²UMF, Iasi, Romania

In our clinical study, prevalence of post-surgical sepsis represent 7.01% of the surgical operations for colorectal cancer. The other abdominal complications are eviscerations, post-surgical occlusions and residual abscesses.

Objectives: Our study try to evaluate the prevalence of postoperative peritonitis occurring surgeries of colorectal cancer in relation with their etiology and clinic outcome.

Material and methods: We conducted a retrospective observational study over a period of ten years. We have to analyze the occurrence, etiology, to diagnose and surgically manage a sample of 25 cases of intraabdominal sepsis occurring following 147 surgeries of colorectal cancer. The semiology of a postoperative peritonitis is easy to spot in the young age patients due to the responses occurring a few days after the surgeries: pain in the abdominal area, confined to an area in which palpation shows contraction. In a few hours the pain diffuses. Fever, nausea, vomiting and all the clinical signs of peritonitis then occur.

Results: In our study, the highest prevalence of postoperative sepsis was found following surgical treatment of colorectal cancer. The global fatality rate on our sample of post-surgical peritonitis is 20%. We have considered this level in comparison with data from a similar experiment with an average fatality rate of up to 90%. In 4 cases we performed multiple surgeries and in two such cases, our patients deceased. Our average of surgeries per case was three. In comparison with the first surgery for neglected peritonitis, in the cases that we performed the surgery for the second time and subsequent, we changed our operating plans in order for the procedure to unfold as quickly as possible, having in mind the risk of death the patients were subject to.

Conclusions: It is difficult to establish quickly a diagnosis of post-surgical peritonitis only based on the clinical signs. Moreover, one must exert a great amount care and analyze all clinical data in concurrence with the laboratory tests and analyses and the X-ray examinations as all the necessary data must be compounded in the diagnosis.

Key words: Post-surgical peritonitis, colorectal cancer.
MMP-9 is a strong prognostic survival marker in rectal carcinoma

Saulius Svagzdys¹, Vaiva Lesauskaite², Zilvinas Saladzinskas¹, Algimantas Tamelis¹, Dainius Pavalkis¹
¹Clinic of Surgery, Academy of Medicine, Lithuanian University of Health Science,
²Institute of Cardiology, Academy of Medicine, Lithuanian University of Health Science, Kaunas, Lithuania

Introduction: Common prognostic factors do not fully predict clinical outcomes in colorectal cancer, one of the most common malignancies in developed countries. Therefore, biological prognostic markers are under investigation. We investigated the prognostic value of expression of matrix metalloproteinases (MMP-2 and -9) and their inhibitors (TIMP-2 and -3) in rectal carcinoma to predict survival of the patients.

Methods: Retrospective analysis of clinicopathological findings of 64 patients who underwent rectal resection due to carcinoma and were followed-up from 2 to 96 months was performed. Semi-quantitative scoring was used to assess expression of MMP-2 and -9 and TIMP-2 and -3 in rectal carcinoma.

Results: During the follow-up, 28 patients died. The deceased patients demonstrated significantly higher expression of MMP-9 and lower expression of TIMP-3 in parenchymal and lower expression of TIMP-2 in stromal cells of carcinoma, compared to survivors. Moreover, the deceased patients were associated with advanced tumor, lymph nodes and distant metastases. According to univariate analysis longer survival was predicted by lower expression of MMP-9 in parenchymal cells, tumor size (early tumor), absence of lymph nodes or distant metastases. Multivariate analysis revealed that lymph nodes metastases, higher expression of MMP-9 in parenchymal, and lower expression of MMP-9 in stromal cells significantly increased mortality.

Discussion/Conclusion: Expression of MMP-9 in rectal carcinoma parenchymal cells is a strong prognostic marker for overall survival. It is important to identify the source of MMP-9 in order to predict better overall survival of the patients.
N-acetylcysteine has a powerful dual effect of anti-inflammatory and antioxidant activities resulting in complete improvement of acetic acid-induced colitis in rats

Veysel Tahan¹, Associate Professor, M.D., Suleyman Uraz¹, Fellow, M.D., Gulgun Tahan¹, Fellow, M.D., Huseyin Aytekin², Fellow, M.D.
¹University of Pittsburgh, Department of Pathology Pittsburgh, PA, USA
²Istanbul University Cerrahpasa Medical Faculty, Department of Internal Medicine, Istanbul, Turkey

Introduction: Increased free-radical production, decreased antioxidant capacity, and excessive inflammation are well known features in the pathogenesis of inflammatory bowel disease. NAC is a powerful antioxidant and a scavenger of hydroxyl radicals. N-acetylcysteine has also been shown to have anti-inflammatory activities in tissues. Our study objective is to investigate the effects of N-acetylcysteine on tissue inflammatory activities using an ulcerative colitis (UC) model induced by acetic acid (AA) in rats.

Methods: Wistar rats (n = 32) were divided into four groups. AA-induced colitis was performed in two of the groups, while the other two groups were injected with saline intrarectally. One of the AA-induced colitis groups and one of the control groups were administered 500 mg/kg/day N-acetylcysteine intrarectally, and the pair groups were given saline. After 4 days, colonic changes were evaluated biochemically by measuring proinflammatory cytokines (tumor necrosis factor [TNF]-α, interleukin [IL]-1β, and IL-6), myeloperoxidase (MPO), malondialdehyde (MDA), glutathione (GSH), and superoxide dismutase (SOD) levels in tissue homogenates and by histopathological examination.

Results: AA caused colonic mucosal injury, whereas N-acetylcysteine suppressed these changes in the AA-induced colitis group (p < 0.001). AA administration resulted in increased TNF-α, IL-1β, IL-6, MPO, and MDA levels, and decreased GSH and SOD levels, whereas N-acetylcysteine administration reversed these effects (all p < 0.001).

Discussion/Conclusion: The present study proposes that N-acetylcysteine has a powerful dual action as an effective anti-inflammatory and an antioxidant, and may be a hopeful therapeutic agent for UC.
Prognostic value and prediction of the presence of KRAS mutation on the basis of combined pathology data of colorectal cancer

A. Tertychnyy¹, G. De Hertogh², X. Sagaert², K. Geboes²
¹First Moscow Medical University, Moscow, Russia; ²UZ, Leuven, Belgium

Introduction: Therapeutic agents targeting epidermal growth factor receptor (EGFR) improved outcomes for colorectal carcinoma. However, mutations in KRAS gene negatively predict success of therapy. The relation between KRAS mutation status and pathological features of CRC has not been explored in depth. The aim of the present study was to compare pathological grading systems and other features with KRAS status of tumors.

Methods: We investigated surgical biopsies of 154 CRC patients with ordinary adenocarcinomas. One HE stained slide was used for cancer grading following the classical 2-tiered or 4-tiered scheme and the Nottingham Breast Cancer Grading System (NGS). Other parameters included: tumor margin, budding, desmoplasia, lymphocytic infiltrate, and vascular or perineural invasion. Serial slides were used for testing for KRAS mutations (G12D, G12V, G13D, G12C, G12A, G12S and G12R). Presence or absence of mutations was correlated with the features of the tumors.

Results: KRAS mutations were identified in 69 (44.8%) cases with a significant correlation between increasing tumor grade and decreasing KRAS mutation frequency ($p < 0.05$). There was a trend towards association of budding and desmoplasia with KRAS mutation and a significant correlation between increasing NGS grade and decreasing KRAS mutation frequency ($p < 0.05$).

Discussion/Conclusion: Adenocarcinoma showing less than 10% tubule formation has only 1 in 5 chance of being KRAS mutated, whereas more gland formation is associated with 1 in 2 chance. Application of the NGS grade is therefore useful. Medullary and signet-ring cell carcinomas have a very low chance of mutation. These tumor types have generally less good prognosis. Therefore early use of new EGFR targeting therapy in such cases is reasonable.
Single direct suture of the perineal wound after cylindrical abdominoperineal exstirpation of the rectum (Holm-procedure)
- An alternative to a Mesh or flap technique

W. Thasler, M. Kreis
Department of Surgery, LMU Grosshadern Hospital, Munich, Germany

Introduction: The abdomino-perineal exstirpation of the rectum leads to an increase in perforation, R1 resections and local recurrence compared to sphincter-preserving anterior rectum resection. The Holm-procedure known as the cylindrical abdominoperineal rectum exstirpation creates a larger circumferential soft tissue cover, resulting in a larger perineal defect of the pelvic floor, which will commonly lead to the necessity of performing a Mesh or rotation flap procedure. The aim of this study was to evaluate if a simple perineal direct suture of the sub-cutis and cutis is a sufficient closure for the pelvic floor after cylindrical abdominoperineal exstirpation.

Methods: Following cylindrical abdominoperineal rectum exstirpation, 16 consecutive patients (6 females and 10 males with a median age of 64 years) were recruited between November 2008 and December 2010 for this study. 10 out of 16 patients were pre-treated by neoadjuvant chemotherapy. Patients were following up for a period of 16 ± 7 month.

Results: In two cases, a R1 resection at the circumferential resection margin was detected postoperatively. Wound healing of the sacral wound was disturbed in 38% of the cases. In 80% of these patients, an open wound treatment was successful in closing the defect during this time. A vacuum closure was performed in one patient and two patients developed a wound infection of the abdominal wall incision.

Conclusion: The rate of wound healing disturbance at the pelvic floor after cylindrical abdominoperineal rectum exstirpation is high but all wounds could be treated conservatively. Perineal hernias did not occur during the observation period of one and a half year. The closure of the pelvic floor by direct suturing of the cutis and sub-cutis after cylindrical rectum exstirpation seems to be a simple alternative compared to the more complex closure using Mesh fixation or the rotation flap technique.
Association of caspase-8 and -9 gene polymorphisms and colorectal cancer susceptibility and prognosis

George E. Theodoropoulos, Maria Gazouli, Anna Vaiopoulou, Nikolaos Nikiteas
1st Dept of Propaedeutic Surgery and Biology Dept of Athens Medical School, Athens, Greece

Introduction: Caspase-8 (CASP8) and -9 (CASP9) play crucial roles in regulating apoptosis, and their functional polymorphisms may alter cancer risk. Our aim was to investigate the association between CASP8 and CASP9 gene polymorphisms and colorectal cancer (CRC) susceptibility.

Methods: A case-control study at 402 CRC patients and 480 healthy controls was undertaken in order to investigate the association between the genotype and allelic frequencies of CASP8-652 6N ins/del and CASP9-1263 A>G polymorphisms and the CRC susceptibility. The polymerase chain reaction (PCR) restriction fragment length polymorphism method was used and the incidence of polymorphisms on messenger RNA (mRNA) expression levels was detected by quantitative reverse-transcriptase PCR in CRC tissues.

Results: No statistical significant association was observed between CASP8-652 6N ins/del polymorphism frequencies and CRC susceptibility. CASP9-1263 G allele was observed to be significant associated with reduced risk of CRC (p value; OR [95% CI] < 0.0001; 0.61 [0.51–0.74]). Homozygotes for the -1263 GG CASP9 genotype, and hetrozygotes for the -1263 AG genotype expressed 6.64- and 3.69-fold higher mRNA levels of Caspase-9, respectively compared to the -1263 AA genotype cases. No significant association was observed between CASP9-1263 A>G polymorphism and tumor characteristics. The CASP9-1263 GG genotype was associated with increased overall survival in CRC patients (p = 0.04). TNM stage and -1263 AA CASP9 were revealed as independent prognostic factors.

Discussion/Conclusion: The CASP9-1263 A>G polymorphism was observed to play a protective role in CRC predisposition, while the CASP9-1263 GG genotype may confer a better prognosis at CRC patients.
Results of extralevator abdomino-perineal resections for rectal cancer (multicenter study)

P.V. Tsarkov¹, I.A. Nechay², D.A. Hubezov³, V.V. Polovinkin⁴, Y.M. Makeev⁵, A.M. Karachun²,⁶, I.A. Tulina¹, M.A. Danilov¹, I.S. Tsarkov⁵
¹Russian Research Center of Surgery n. a. acad. B.V. Petrovsky, Department of Colorectal and Pelvic Floor Surgery, Moscow, Russia; ²The City Hospital #40, St. Petersburg, Russia; ³Regional Hospital, Ryazan, Russia; ⁴Regional Clinical Hospital # 1. n. a. Prof. S. Ochapovsky, Krasnodar, Russia; ⁵Regional Oncology Center, Balashikha, Russia; ⁶Leningrad Regional Oncology Center, St. Petersburg, Russia

Background: One of the causes of local recurrence after conventional simultaneous abdomino-perineal resection (APR) of the rectum is a high incidence of inadvertent tumor perforation (ITP) and positive circumferential resection margins (CRM). In order to reduce the frequency ITP and CRM a new technique of extralevator APR (eAPR) was proposed. During the abdominal phase the rectum is dissected according to the principles of total mesorectal excision no farther than the level of the lower boundary of the pelvic plexus. This helps to prevent coning of the specimen and reduce the risk of tumor perforation. Transperineal resection after patient turnover to prone position is performed with wide excision of levator muscles, that stay attached to the rectum and ensure additional layer of protection in the level of the tumor.

Objective: This study aims to evaluate radicality and immediate results of eAPR compared to traditional APR (tAPR).

Materials and methods: Five centers participated in the study. The results of 125 eAPR consequently performed in 2009–2011 for low rectal cancer were compared to 130 traditional APR in consequent retrospective patients.

Results: The groups didn't differ in male/female ratio (75/50 in eAPR and 62/68 in tAPR) and average age (0.06). The tAPR and eAPR did not differ significantly in average duration of operations (290.2 ± 89.2 min and 317.2 ± 124.2 min respectively, p = 0.07), but average blood loss was significantly greater in tAPR (568.0 ± 556.7 ml and 378.9 ± 515.3 ml respectively, p = 0.01). Various postoperative complications were observed more frequently in tAPR than in eAPR (48% vs. 38%, p = 0.1). Perineal wounds infection was seen more often after tAPR than after eAPR (21% and 11%, p = 0.03). Postoperative bleeding was observed only among patients in tAPR group: 4 patients had intra-abdominal bleeding, 3 – perineal wound bleeding. Thirty-day mortality was 0% in eAPR and 6% in the tAPR (p = 0.02). The technique of eAPR compared to tAPR helped to significantly reduce the frequency of ITP (4% vs. 11%, p = 0.01) and positive CRM (6% vs. 16%, p = 0.04).

Conclusion: Lower intraoperative blood loss, fewer postoperative complications and absence of mortality demonstrate safety and feasibility of eAPR. Lower incidence of ITP and positive CRM indicate potential better oncological results of eAPR compared to tAPR.
D3 lymph node dissection in right colon cancer: Too much or just enough?

Petr Tsarkov, M.D., Ph.D., Badma Bashankaev, M.D., Alexander Kravchenko, M.D., Inna Tulina, M.D.
Department of Colorectal and Pelvic Floor Surgery, Russian Research Center of Surgery named after B.V. Petrovsky, Moscow, Russia

Standard surgical treatment of right colon cancers is associated with worse survival than results of left colon cases. Principles of total mesorectum excision could be beneficial in right colon cancer management. Mesocolon excision with D3 lymph node dissection (LND) in cases of right hemicolectomy is proposed as a way that provides negative resection margins of mesocolon envelope with maximum harvested lymph nodes (LN). It's safety and effectiveness was evaluated.

Methods: A retrospective review of a prospectively collected database from 07/2006–01/2010 was performed. Right hemicolectomy cases with D3 lymph node dissection for cancer were identified. Study variables included patient’s demographics, preoperative, intraoperative, postoperative mortality, morbidity data, pathology results with number, positivity of harvested LN were evaluated. Follow up data was obtained through telephone conversation.

Results: Study included 49 patients (28 females), 14 with metastasis. Mean age 63.1 years, mean BMI – 27.3 kg/m². Mean ASA score – 3.2. Mean OR time -157 min with mean dissection time 61.4 min. Mean hospital stay was 21 days, postoperatively – 12 days. There were no 30-day mortality.

Mean number of harvested LN – 24.8. 17 patients had mean 3.4 positive LN. All patients with distant metastasis had mean number of 5.2 positive LN.

Ninety percent of patients were available with mean length follow up of 14.9 months. Overall survival rate was 77.8%, in group without metastasis – 92.8%, in the group with distant metastasis – 24.2%. There were no survival difference in the groups with negative LN and positive LN (88.6% vs. 76.1%, p = 0.9).

Conclusions: D3 lymph nodes dissection in right colon cancer is safe method of radical oncologic resection that provides survival benefits in group of patients with positive LN. However, studies in a larger patient population with longer follow up are required to demonstrate benefits of this complex technique.
The effectiveness of the multidisciplinary approach in elective surgery of colorectal cancer in elderly patients

P.V. Tsarkov, V.V. Nikoda, V.I. Stamov, D.R. Markar’yan, I.A. Tulina
Russian Research Center of Surgery, Moscow, Russia

Introduction: Publications of the last decade indicate a steady rise of colorectal cancer all over the world. Colorectal cancer is on the second place in the structure of oncological mortality in developed countries, including Russia. The majority of colorectal cancer deaths (up to 50%) occur in elderly, which are 75 years and older. The octogenarians are more likely to have comorbidities and age-specific deteriorating organ function, which could make their tolerance of surgery.

Aim: To determine the short- and long-term outcomes of the multidisciplinary approach in elective colorectal surgery in patients ≥ 75 years of age.

Methods: A review of 70 octogenarians who underwent colorectal cancer surgery between April 2006 and November 2010 was performed from prospectively collected database. The median age was 79 (75–79) years. Every patient was examined by multidisciplinary team before surgery and after. Conservative therapy was prescribed or corrected if any organ failure detected. Comorbidities were quantified using the weighted Charlson Comorbidity Index and ASA classification. CR-POSSUM scores and the predicted mortality rates were calculated. Outcome measures were morbidity rates and 30-day mortality rates.

Results: The mean index of comorbidity was 7.1 (6–11) and 79% of patients were classified ASA III and above. Moderate and severe decompensation of comorbidity was detected in 46% of patients. Most frequently observed ailments were cardiovascular – 31%. The mean predicted mortality rate based on CR-POSSUM scoring model was 12.8%. All patients with comorbidities were treated conservatively before surgery during mean period of 12.2 days, nine patients (13%) required implantations of pacemakers to control heart rate in perioperative period. In 64 (91%) cases surgical resection of the colon or rectum with primary anastomosis were performed, in 6 (9%) – abdominoperineal resection of the rectum and in two cases – Hartmann’s operation. Postoperative complications (surgical) were noticed in 40 (57%) cases. Postoperative mortality rate (death within 30 days after surgery) was 5.7%, the 2- and 3-year overall survival rate (according to Kaplan and Meier) was 77.4 ± 5.6% and 72.9 ± 6.3% respectively.

Conclusion: Using the multidisciplinary approach in the management of elderly allows reaching the acceptable mortality level (5.7% in comparison with predicted 14.8%) and high 2- and 3-year survival rates. This means that chronological age alone should not be contraindication to the elective curative surgery of colorectal cancer in elderly if overall assessment of the perioperative risk is possible.
Pretherapeutic selection of the most promising drugs for the individual CRC patient using the functional Spheroid Microtumor Model

University of Munich, LMU, Department of Surgery-Großhadern, *SpheroTec GmbH, Munich, Germany

**Introduction**: Despite significant advances in conventional therapy, the 5-year survival rate of CRC patients with a R0 resection is less than 50%. Above all, most of the patients develop metastases under chemotherapy. Thus, a diagnostic tool to select CRC patients for the most efficient therapy is urgently needed.

**Methods**: A monocenter cohort study enclosing 58 CRC patients at UICC stage II and III was initiated. From the primary tumor samples multicellular spheroids were generated and treated with standard cytotoxic drugs, i.e. 5-FU, oxaliplatin, irinotecan and Cetuximab. The cytotoxic effects of the drugs on both tumor cells and stromal cells were tested using flow cytometry after 96h treatment.

**Results**: Spheroids could be generated from all solid patient tumor samples tested. A minimum of 500 mg tumor tissue is required to form a sufficient number of spheroids to test all drug combinations. In a special tissue conserving medium tumor samples could be transported over 60 h without loss of vitality. A high portion of vital cells is necessary for the capability of spheroid formation. Comparison between tumor tissue and spheroid model revealed that 89% of the spheroids closely mimicked the cellular composition, the target based biomarker profile and the immune status of the original cancers. Most important, patient spheroids allow the selection of the most effective drugs in mono- and combination therapy. This includes standard chemotherapeutics as well as antibodies and small molecule inhibitors.

**Discussion/Conclusion**: The Spheroid Microtumor Model generated from cancer tissue closely reflects the complexity and heterogeneity of the individual patient tumor. Thus it represents a valid diagnostic test system for individualizing cancer therapy.
Erythropoietin receptor expression in colorectal cancer – Immunohistochemical and mRNA studies – In perspective of treatment with recombinant EPO in colorectal cancer-associated anemia

Andrzej Wincewicz¹, Chris P. Miller², Carl Anthony Blau², Urszula Sulikowska¹, Stanislaw Sulikowski³
¹Specialist Medical Practice – Pathologist, Bialystok, Poland; ²Department of Medicine/Hematology and the Institute for Stem Cell and Regenerative Medicine, University of Washington, Seattle, WA, USA; ³Department of General Pathomorphology, Medical University of Bialystok, Bialystok, Poland

Introduction: Cancers can produce erythropoietin (EPO) and some of them also harbour receptor of erythropoietin (EPOR). If so, a serious question should be raised: Does EPOR cancer tissue respond to EPO in same manner as red blood cells precursors in the blood marrow? Physiologically, EPO is produced in response to hypoxia which is associated with anaemia as a result of decrease of circulating RBC. Similarly, cancers are hypoxic due to insufficient vascularisation of tumors. Lately we have reported in Falk Symposium 174 communication that patients with higher EPO levels were characterized by significantly shorter overall survival than patients with lower levels of the marker. Therefore we aimed at careful and reliable evaluation of EPOR in colorectal cancer.

Methods: We applied C20 antibody to stain EPOR in 136 colorectal cancers. Moreover, 118 formalin-fixed paraffin-embedded (FFPE) tumor samples of colorectal cancer were destined for mRNA EPOR evaluation. Firstly, RNA was extracted from FFPE tumor sections using the Absolutely RNA FFPE kit (Strata-gene, La Jolla, CA, http://www.stratagene.com). Next, cDNA targets were amplified using Taqman probes and a 7900HT thermal cycler (Applied Biosystems, ABI, Foster City, CA, http://www.applied-biosystems.com). Relative quantification was determined using the comparative Ct method, 2-ΔCT where ΔCt = mean Ct for target gene – mean Ct for reference gene. Reference gene stability was evaluated using the Genorm algorithm.

Results: EPOR staining was positive in 61 (44.8%) of examined colorectal cancers. However, it was found that this antibody C20 antibody to EPOR can also cross-react with HSP70. Due to unsatisfactory preservation of mRNA in studied 118 samples, only 33 of them showed EPO mRNA (28%). However, it was not possible to use the mRNA data from these 33 samples for correlative analysis with other clinical variables as there was a clear biasing effect of RNA abundance/integrity on EpoR mRNA level, even after normalization.

Discussion/Conclusion: Considering a limited specificity of this antibody to detect EPOR, membranous positivity of C20 is more likely to be of EPOR while cytoplasmic staining can be of HSP70. Our results of mRNA evaluation show the presence of EPOR expression in human colorectal cancer. It should be clearly stated that at least an essential rate of these tumors harbour EPOR receptor. Thus, colorectal cancer is EPO sensitive tissue and the trophic impact of EPO is highly probable on colorectal
cancer growth. In the light of our findings, exogenous EPO administration should not be given to treat anaemia of colorectal cancer patients, unless EPOR status is determined in colorectal cancer tissue of patients who are considered to be given recombinant EPO treatment.
The role of capsule endoscopy in evaluating and managing small bowel disorders

Edward Yoong¹, Dr Kadukkavil Padmakumar²
¹Medical Student, School of Medicine, University of Manchester, Manchester, Greater Manchester, UK
²Consultant, Department of Gastroenterology, Bolton NHS Foundation Trust, Bolton, Lancashire, UK

Introduction: The small bowel has always been a challenging area for the gastroenterologist to investigate. Currently, no gold standard exists; a combination of methods is used to diagnose small bowel pathology. Capsule endoscopy (CE), is an innovative, non-invasive method of visualising the entire small bowel, however, it is not routinely performed due to expense.

58 CE patients from the Royal Bolton Hospital were audited against guidelines based on the British Society of Gastroenterologists (BSG) 2007, reviewing whether this investigation has a positive influence in clinical outcome.

Methods: Case notes of those requiring CE from January 2007–June 2011 were studied retrospectively. Inclusion criteria included a negative oesophagogastrroduodenoscopy, colonoscopy, or barium follow-through.

The indication, presenting complaint, and blood transfusion requirement were all noted, as were results of all prior investigations.

Results: CE confirmed a diagnosis in 15 (26%). The cause for obscure gastrointestinal bleeding was discovered in 11 (29% of patients indicated), Crohn’s disease (CD) was confirmed in 3 (21%). It found a cause for chronic abdominal pain in one patient (2%), which was CD.

Abnormal results were discovered in 19 (33%); which were found to angiodysplasia (7), CD (6), polyps (2), nodular lymphoid hyperplasia (1), distorted villi (1), coeliac (1), ulceration (1).

Discussion/Conclusion: The diagnostic yield is comparable to other studies carried out with similar sample sizes. CE found the cause of OGIS in 29% and confirmed CD in 21% indicated, when other modalities could not, influencing clinical outcome. There may be a more prominent role for CE in future clinical practice.
**Stomach and colon cancer diagnosis of vitamin B12 and folic acid levels**

E. Yorulmaz\(^1\), V. Cakici\(^2\), C. Ulasoglu\(^1\), M. Celik\(^2\), I. Tuncer\(^1\), H. Ciftci\(^2\)

\(^1\)Department of Gastroenterology, Goztepe Training and Research Hospital, Istanbul, Turkey
\(^2\)Department of Internal Medicine, Goztepe Training and Research Hospital, Istanbul, Turkey

Vitamin B12 and folic acid which is necessary for cell division and DNA replication in the construction of two important vitamin. In this study, vitamin B12 and folic acid levels in the diagnosis of stomach and colon cancer and liver metastasis was aimed to determine the effectiveness in demonstrating.

The study, 16 men, 15 women (mean age 68.19 ± 12.05) 31 colon cancer, 20 men, 10 women (mean age 65.13 ± 13.39) 30 stomach cancer and 16 men, 14 women (average age 65.36 ± 11.79) were 30 healthy control subjects. Users of vitamin prepare previously, another well-known disease and those with a history of surgery were excluded. Computerize tomography examination of liver metastases in patients evaluated, compared with vitamin B12 and folic acid levels.

Stomach cancer, 12 patients (40%), colon cancer in 8 patients (25.8%) had liver metastases. Values of folic acid cancer group were significantly lower than the control group (p < 0.01), while vitamin B12 levels were significantly higher (p < 0.05). In the group with liver metastasis in stomach cancer patients without liver metastasis group than the high level of vitamin B12, although there was no significant relationship (p > 0.05). In the group with vitamin B12 levels in patients with colon cancer liver metastasis, was significantly higher than those without metastasis (p < 0.05). Stomach and colon cancer patients with metastasis was no significant relationship folic acid levels (p > 0.05).

High vitamin B12 level may be a parameter indicating the stomach and colon cancer liver metastasis. The prevention of stomach and colon cancer, the effectiveness of folic acid replacement in the number of patients, more studies are needed.
Local recurrence rate in rectal cancer

W. Zaglmaier, H. Wundsam, K. Rohregger, G. Pressl, M. Aufschnaiter, K. Emmanuel
Abteilung für Allgemein- und Viszeralchirurgie KH der Barmherzigen Schwestern
Linz, Austria

Background: The recurrence rate in rectal cancer has been lowered throughout the last years by performing adequate TME/PME routinely and using neo-adjuvant therapy strategies in UICC II and beyond tumors.

Methods: We retrospectively analyzed the outcome data (local recurrence rate depending on tumor stage, localization and method of resection) of all our oncological patients who underwent surgery for rectal cancer from 2000 to 2010 (i.e. a number of 402).

Afterwards we focused on APR and compared our data to the results of T. Holm (Karolinska University of Stockholm) and other international data to see whether an extended form of APR could additionally lower the local recurrence rate.

Conclusion: We could illustrate that APR with nicely done TME in combination with chemoradiotherapy in low rectal cancer can have as good results (6.1% local recurrence rate at BHS Linz after 12 months) as the much more invasive and mutilating extended APR (7.15% local recurrence rate at the Karolinska Institute in Stockholm after 16 months – T. Holm, 2008).
Individual CRC-tumor-ID by combining biomarker profiling and functional 3D drug testing

M. Zoller, J. Gülden, M. Joka, I. Funke*, K.-W. Jauch, B. Mayer
Clinic of the University of Munich, LMU, Department of Surgery-GH, *SpheroTec GmbH, Munich, Germany

Introduction: Despite R0-resection followed by chemotherapy, tumor-associated mortality in colorectal cancer patients is high. Aiming towards a more effective chemotherapy, tumor biology of the individual patient was analyzed combining a predictive and resistant biomarker profile with functional 3D drug testing.

Methods: Protein as well as molecular biomarkers were analyzed in 45 CRC patients by IHC, DNA isolation, PCR and pyrosequencing. Functional drug testing was performed in patient spheroids prepared from fresh tumor samples. Efficacy of standard therapies was analyzed by FACS analysis. Statistics was performed using SPSS.

Results: HER2/neu expression was detected in 51% of the primary tumors, 13.3% showed the therapy relevant score 3+. However Trastuzumab resistance was observed in 38% of strong HER2/neu positive tumors. Promising for immunotherapy high EpCAM (> 90%) expression was found in all tumors. Nevertheless in addition to the strong target expression, the fraction of CD45+ cells had a high impact on Removab response. EGFR expression was observed in 95.6%, while KRAS mutation was detected in 41.7%. Response to Cetuximab therapy revealed that not each KRAS mutation showed a similar sensitivity in the 3D model.

Discussion/Conclusion: In the biomarker profile HER2/neu is shown as a potential new target in CRC therapy. In addition the spheroid model promises to play a superior role for drug selection. Due to the complex pathophysiology, it is not possible to highlight one single biomarker for one drug. A multimodal tumor testing is necessary to identify the individual CRC tumor ID for each patient to choose the most effective chemotherapy.
<table>
<thead>
<tr>
<th>Name</th>
<th>Poster Numbers</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Adamina, M.</td>
<td>1</td>
<td>Danilov, M.A.</td>
<td>71</td>
</tr>
<tr>
<td>Alekseev, M.</td>
<td>2</td>
<td>De Hertogh, G.</td>
<td>68</td>
</tr>
<tr>
<td>Anagnou, N.P.</td>
<td>20</td>
<td>Demir, I.E.</td>
<td>35</td>
</tr>
<tr>
<td>Aufschnaiter, M.</td>
<td>78</td>
<td>Dereniewicz-</td>
<td>12</td>
</tr>
<tr>
<td>Aytekin, H.</td>
<td>67</td>
<td>Winczewicz, R.</td>
<td></td>
</tr>
<tr>
<td>Bachmann, L.</td>
<td>38</td>
<td>Doll, D.</td>
<td>29</td>
</tr>
<tr>
<td>Backert, I.</td>
<td>43</td>
<td>Domso, M.</td>
<td>42</td>
</tr>
<tr>
<td>Badea, A.</td>
<td>4, 5, 21</td>
<td>Dristich, P.</td>
<td>7, 8, 63, 64</td>
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<tr>
<td>Badea, D.</td>
<td>3, 4, 5, 21, 22</td>
<td>Droeser, R.</td>
<td>14</td>
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<td>Badea, M.</td>
<td>3, 4, 5, 21</td>
<td>Droshneva, I.</td>
<td>55</td>
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<td>Bader, F.G.</td>
<td>44, 45</td>
<td>Dumitrascu, T.</td>
<td>15</td>
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<td>6</td>
<td>Duta, D.</td>
<td>4, 5</td>
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<tr>
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<td>45</td>
<td>Eftimie, M.</td>
<td>60</td>
</tr>
<tr>
<td>Basdanis, G.</td>
<td>46</td>
<td>Ehrmann, J.</td>
<td>31</td>
</tr>
<tr>
<td>Bashankaev, B.</td>
<td>72</td>
<td>Emmanuel, K.</td>
<td>78</td>
</tr>
<tr>
<td>Basilicata, G.</td>
<td>48</td>
<td>Eppenberger-</td>
<td>14</td>
</tr>
<tr>
<td>Bauerfeind, P.</td>
<td>38, 40</td>
<td>Castori, S.</td>
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<tr>
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<td>41, 43</td>
<td></td>
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<td>35</td>
<td></td>
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<td>6</td>
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<td>16</td>
</tr>
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<td>Benes, M.</td>
<td>7, 8, 63, 64</td>
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<td>17, 18</td>
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<td>40</td>
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<td>17, 18</td>
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<td>47</td>
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<td>75</td>
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<td>19, 26</td>
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<td>24</td>
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<td>14</td>
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<td>55</td>
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<td>38</td>
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<td>35</td>
<td>Friess, H.</td>
<td>13, 32, 35, 36,</td>
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<td>9</td>
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<td>37, 44, 45, 54,</td>
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<td>38</td>
<td></td>
<td>62</td>
</tr>
<tr>
<td>Büchler, M.</td>
<td>9</td>
<td>Funke, I.</td>
<td>74, 79</td>
</tr>
<tr>
<td>Buhr, H.J.</td>
<td>23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buiga, R.</td>
<td>42</td>
<td>Gazouli, M.</td>
<td>20, 27, 70</td>
</tr>
<tr>
<td>Cakici, V.</td>
<td>77</td>
<td>Geboes, K.</td>
<td>68</td>
</tr>
<tr>
<td>Carausu, M.</td>
<td>65</td>
<td>Geist, C.</td>
<td>6</td>
</tr>
<tr>
<td>Cazacu, M.</td>
<td>42</td>
<td>Gennatas, K.</td>
<td>47</td>
</tr>
<tr>
<td>Celik, M.</td>
<td>77</td>
<td>Genunchescu-</td>
<td>3, 4, 5, 21, 22</td>
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<tr>
<td>Ceyhan, G.</td>
<td>32, 35</td>
<td>Dumitrescu, A.</td>
<td></td>
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<tr>
<td>Cha, B.K.</td>
<td>11</td>
<td>Gertler, R.</td>
<td>32, 36</td>
</tr>
<tr>
<td>Chang, S.K.</td>
<td>11</td>
<td>Gohda, K.</td>
<td>62</td>
</tr>
<tr>
<td>Chernyshov, S.</td>
<td>10, 51, 57</td>
<td>Gröne, J.</td>
<td>23</td>
</tr>
<tr>
<td>Choi, C.H.</td>
<td>11</td>
<td>Gülde, J.</td>
<td>24, 79</td>
</tr>
<tr>
<td>Ciftci, H.</td>
<td>77</td>
<td>Heberer, M.</td>
<td>14</td>
</tr>
<tr>
<td>Csobán, T.</td>
<td>30</td>
<td>Henne-Bruns, D.</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hirt, C.</td>
<td>14</td>
</tr>
</tbody>
</table>
Holtorf, A. 25  Lee, L. 23
Holzmann, B. 25  Lesauskaite, V. 50, 66
Hubezov, D.A.  Liebl, F. 35
Hul, T. 7, 8, 63, 64  Liefers, G. 56
Hummel, B. 1  Lizdenis, P. 33, 49
Hunold, F. 38  Loos, M. 36, 54
Iezzi, G. 14  Ludwig, C. 74
Ilías, T. 19, 26  Lugli, A. 14
Ionescu, M. 15  Maak, M. 13, 32, 35, 37,
Iordache, D. 5  44, 54, 62
Ishihara, H. 62  Makeev, Y.M.
Janssens, K.-P. 25, 29, 37, 44, 45, 62  Manser, C. 38, 40
Jauch, K.-W. 24, 74, 79  Marbet, U.A. 38
Johannes, L. 37  Marenich, N.S. 39
Joka, M. 24, 74, 79  Markan'yian, D.R. 73
Jung, A. 6  Martini, M. 25
Kahlert, C. 9  Matsushima, T. 62
Kamenar, D. 63  Mayer, B. 24, 74, 79
Kanczuga-Koda, L. 12  Meier, M. 59
Karachun, A.M.  Mikaterfale, C.
Karamanlis, E. 46  Michalopoulos, A. 46
Karamanolis, G. 27  Mihaila, R.G. 19
Kashnikov, V. 34  Miller, C. 75
Kathy, S. 28, 30  Misselwitz, B. 40
Keerl, A. 36, 58  Mittrut, P. 21, 22
Kehl, T. 35  Movadat, O. 41
Keller, L. 29  Muresan, F. 42
Kincses, Z. 28, 30
Kircher, A. 9  Näf, F. 1
Koch, M. 9  Nakayama, S. 62
Kocher, T. 36, 58  Nechay, I.A. 71
Koda, M. 12  Neufer, C. 43
Konecny, M. 31  Neurath, M.F. 41, 43
Konovalov, D.M. 39  Niemetz, T. 9
Kornmann, M. 59  Nikiteas, N. 20, 70
Kravchenko, A. 72  Nikoda, V.V. 73
Kreis, M.E. 69  Nitsche, U. 13, 32, 36, 37,
Kronshage, T. 6  44, 45, 54, 62
Künzli, B. 32, 44  Nosek, V. 63, 64
Kuppen, P.J.K. 56, 62
Kurata, H. 62  Ochs, C. 29
Langer, R. 13, 35, 44, 54  Oertli, D. 14
Laschinger, M. 35  Padmakumar, K. 76
Latasauskas, T. 33, 49  Panagiototou, D. 46
Lauscher, J. 23  Panidis, S. 46
Lavrinenko, A. 34  Papaconstantinou, I. 47
<table>
<thead>
<tr>
<th>Name</th>
<th>Pages</th>
<th>Name</th>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papadopoulos, V.N.</td>
<td>46</td>
<td>Papailiou, J.</td>
<td>20</td>
</tr>
<tr>
<td>Paramythiotis, D.</td>
<td>46</td>
<td>Pasternak, I.</td>
<td>48</td>
</tr>
<tr>
<td>Pauzas, H.</td>
<td>33, 49</td>
<td>Shelygin, Y.A.</td>
<td>34, 51, 55</td>
</tr>
<tr>
<td>Pavalkis, D.</td>
<td>33, 49, 50, 66</td>
<td>Shemeroskovskii, C.</td>
<td>61</td>
</tr>
<tr>
<td>Peitgen, K.</td>
<td>53</td>
<td>Shibayama, M.</td>
<td>62</td>
</tr>
<tr>
<td>Peresada, I.</td>
<td>51</td>
<td>Shumilova, O.</td>
<td>17, 18</td>
</tr>
<tr>
<td>Petrica, C.</td>
<td>5</td>
<td>Simescu, R.</td>
<td>42</td>
</tr>
<tr>
<td>Pikunov, D.</td>
<td>52</td>
<td>Slotta-Huspenina, J.</td>
<td>44</td>
</tr>
<tr>
<td>Pitt, C.</td>
<td>53</td>
<td>Smyrniotis, V.</td>
<td>47</td>
</tr>
<tr>
<td>Pohle, S.</td>
<td>54</td>
<td>Song, I.D.</td>
<td>11</td>
</tr>
<tr>
<td>Polovinkin, V.V.</td>
<td></td>
<td>Sonnenberg, A.</td>
<td>40</td>
</tr>
<tr>
<td>Polymeneas, G.</td>
<td>47</td>
<td>Spagnoli, G.</td>
<td>14</td>
</tr>
<tr>
<td>Popescu, I.</td>
<td>15</td>
<td>Spicak, J.</td>
<td>7, 8, 63, 64</td>
</tr>
<tr>
<td>Pox, C.</td>
<td>6</td>
<td>Stamat, V.I.</td>
<td>73</td>
</tr>
<tr>
<td>Pressl, G.</td>
<td>78</td>
<td>Statescu, A.</td>
<td>65</td>
</tr>
<tr>
<td>Prochazka, V.</td>
<td>31</td>
<td>Statescu, G.</td>
<td>65</td>
</tr>
<tr>
<td>Puscasu, D.</td>
<td></td>
<td>Stefan, L.</td>
<td>4, 5</td>
</tr>
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</tr>
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<td>36, 54</td>
<td>Stirand, P.</td>
<td>7, 8, 63, 64</td>
</tr>
<tr>
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<td>9</td>
<td>Sulikowska, U.</td>
<td>75</td>
</tr>
<tr>
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<td>55</td>
<td>Sulikowski, S.</td>
<td>12, 75</td>
</tr>
<tr>
<td>Rava, L.</td>
<td>74</td>
<td>Svaigzys, S.</td>
<td>50, 66</td>
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<td>Tertychny, A.S.</td>
<td>39, 68</td>
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<td>2, 34, 52, 57</td>
<td>Thasler, W.</td>
<td>69</td>
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<td>56</td>
<td>Theodoropoulos, G.</td>
<td>20, 27, 70</td>
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<td>Sagaert, X.</td>
<td>68</td>
<td>Theodosopoulos, T.</td>
<td>47</td>
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<td>Sahin, A.</td>
<td>58</td>
<td>Tomulescu, V.</td>
<td>15, 60</td>
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<td>Saladzinskas, Z.</td>
<td>33, 49, 50, 66</td>
<td>Tóth, D.</td>
<td>28, 30</td>
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<td>Samanides, L.</td>
<td>47</td>
<td>Trippel, M.</td>
<td>58</td>
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<td>58</td>
<td>Tsarkov, I.S.</td>
<td>71</td>
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<td>Scheele, J.</td>
<td>59</td>
<td>Tsarkov, P.V.</td>
<td>71, 72, 73</td>
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<td>Tschuppert, S.</td>
<td>58</td>
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<td>Tulina, I.</td>
<td>72, 73</td>
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<td>77</td>
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<td>17, 18</td>
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<td>Urban, O.</td>
<td>63, 64</td>
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<td>43</td>
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<td>41</td>
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<td>7, 8, 63</td>
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<td>78</td>
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<td>63</td>
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<td>56, 62</td>
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