

# Lymph node metastasis of carcinomas of transverse colon including flexures. Consideration of the extramesocolic lymph node stations

Aristotelis Perrakis · Klaus Weber · Susanne Merkel · Klaus Matzel · Abbas Agaimy · Carol Gebbert · Werner Hohenberger

Accepted: 16 July 2014 / Published online: 25 July 2014  
© Springer-Verlag Berlin Heidelberg 2014

## Abstract

**Purpose** Complete mesocolic excision (CME) is nowadays state of the art in the treatment of colon cancer. In cases of carcinoma of transverse colon and of both flexures an extramesocolic lymph node metastasis can be found in the infrapancreatic lymph node region (ILR) and across the gastroepiploic arcade (GLR). These direct metastatic routes were not previously systematically considered. In order to validate our hypothesis of these direct metastatic pathways and to obtain evidence of our approach of including dissection of these areas as part of CME, we initiated a prospective study evaluating these lymph node regions during surgery.

**Methods** Forty-five consecutive patients with primary tumour manifestation in transverse colon and both flexures between May 2010 and January 2013 were prospectively analyzed. Patients were followed up for at least 6 months. Mode of surgery, histopathology, morbidity and mortality were evaluated.

**Results** Twenty-six patients had a carcinoma of transverse colon, 16 patients one of hepatic flexure and four patients one of splenic flexure. The median lymph node yield was 40. Occurrence of lymph node metastasis in ILR was registered in five patients and in GLR in four patients. The mean lymph node ratio was 0.085. Postoperative complications occurred in nine patients, and postoperative mortality was 2 %.

**Conclusions** We were able to demonstrate this novel metastatic route of carcinomas of the transverse colon and of both flexures in ILR and GLR. These could be considered as regional lymph node regions and have to be included into surgery for cancer of the transverse colon including both flexures.

**Keywords** Colon carcinoma · Transverse colon · Hepatic flexure · Splenic flexure · Lymph node · Surgery

## Introduction

The introduction of complete mesocolic excision (CME) for surgical treatment of colon cancer with particular attention to preservation of the mesocolic plane and high tie of the supplying arteries led to significant improved patient outcomes in Erlangen, where 5-year cancer-related survival is now 89 % and the local recurrence rate is less than 4 % after R0 resections [1–4]. Even in advanced cases such as stage III disease, the 5-year cancer-related survival is more than 70 % so that survival rates equal those of rectum carcinoma since total mesorectal excision (TME) was introduced [2, 5–15]. Apart from plane preservation and high tie, the dissection of the pericolic lymph node includes those along a distance of a minimum of 10 cm to both sides of the tumour including the next vascular arcade central wards. However, with transverse colon including both flexures, in advanced cases lymph node metastases can be found along the gastroepiploic arcade right at the greater curvature of the stomach, over the pancreatic head and along the inferior aspect of the left pancreas [1–4]. Therefore, in cancer at that site, a potential “third dimension” of lymphatic spread has to be considered. However, there is no systematic data in the literature on the frequency of the eventual involvement of these nodes. To include these nodes into

---

A. Perrakis and K. Weber contributed equally to this work.

A. Perrakis (✉) · K. Weber · S. Merkel · K. Matzel · W. Hohenberger  
Department of Surgery, University Hospital Erlangen,  
Krankenhausstr. 12, 91054 Erlangen, Germany  
e-mail: aristotelis.perrakis@uk-erlangen.de

A. Agaimy · C. Gebbert  
Institute of Pathology, University Hospital Erlangen,  
Krankenhausstr. 12, 91054 Erlangen, Germany

the lymph node dissection might have a positive impact on outcome. On the other hand, it may increase postoperative complications through the dissection at the pancreatic edge, especially in patients with previous relevant pancreatitis.

However, these lymph node areas are according to the current TNM classification sites of distant metastatic disease.

In order to validate our hypothesis that these areas are parts of regional lymph node metastasis and to get evidence of our approach of including the lymph node dissection of these areas as part of CME in cases of malignancy of transverse colon and of both flexures, we analysed our material prospectively.

### Material and methods

Forty-five consecutive patients with primary invasive carcinomas (at least into the submucosa) of the transverse colon including both flexures were operated between May 2010 and January 2013 and prospectively analyzed. Preoperative findings, data on treatment and histopathological examination were entered for analysis into a standardised database.

Only patients with the following inclusion criteria were selected:

1. No other previous or synchronous malignant tumour
2. Treatment by radical resection with formal regional lymph node dissection
3. No neoadjuvant treatment

Patients with colitis ulcerosa, Crohn disease and familial adenomatous polyposis (FAP) were excluded from this study. Patients and tumour characteristics are demonstrated in Table 1.

Tumour histopathological classification was applied according to the rules of the WHO [16]. Staging followed the seventh edition of the TNM classification [17].

Patients with stage III–IV disease received systemic chemotherapy after surgery.

Locoregional recurrence was defined as recurred carcinoma of the bowel wall or within the lymphatic drainage area in the region of primary tumour, confirmed by clinical and/or pathological examination.

Distant metastases were clinically defined as recurrent tumours in the peritoneum, liver, non-regional lymph nodes or locations outside the abdominal cavity, such as lung and bones. Emergency presentation was defined as bowel obstruction or perforation leading to surgery within 48 h after admission.

Patients were followed up for at least 6 months (range: 6–22 months).

**Table 1** Patients' and tumour characteristics

	Patients ( <i>n</i> )	Percentage (%)
Demographics		
Age mean (years, range)	68.4 (23–91)	
Gender		
Male	27	60
Female	18	40
ASA classification		
ASA I	5	11
ASA II	23	51
ASA III	17	38
Site of tumour		
Transverse colon	26	58
Hepatic flexure	15	33
Splenic flexure	4	9
Surgical mode		
Subtotal colectomy	19	42
Extended right hemicolectomy	26	58
Elective	43	96
Emergency	2	4
Tumour staging		
pT1	1	2
pT2	6	13
pT3	26	58
pT4	12	27
pN0	21	47
pN+	24	53
pN1	13	29
pN2	11	24
ILR	5	11
GLR	4	9
M0	33	73
M1 <sup>a</sup>	12	27
Lymphatic (ILR, GLR)	8	
Peritoneal	7	
Hepatic	1	
Grading		
Well differentiated (G1)	0	0
Moderately differentiated (G2)	21	47
Poorly differentiated (G3)	24	53

ILR infrapancreatic lymph node region, GLR lymph node region right gastroepiploic artery

<sup>a</sup> More than one site of metastasis possible

### Surgical technique

All colectomies were performed as open surgical procedures. A subtotal colectomy with hand sewed end-to-end ascendosigmoidostomy was performed in 19 patients (42 %) and 26 patients (58 %) underwent an extended right

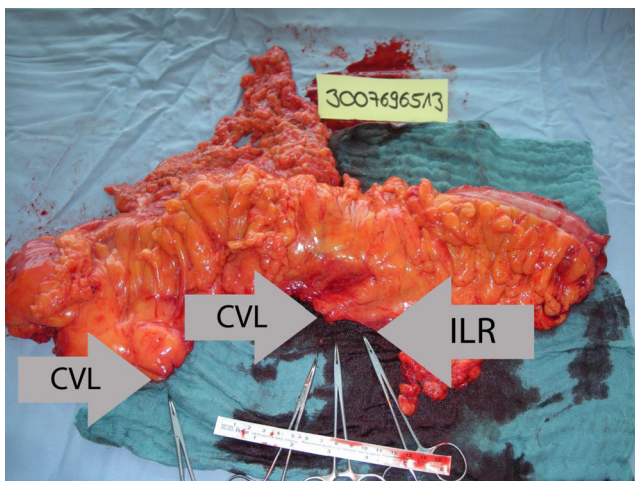
hemicolecotomy with hand sewed end-to-end anastomosis of the terminal ileum to the left transverse colon. In all cases, a radical oncologic resection with CME, CVL and lymph node dissection of the infrapancreatic lymph node region (ILR), skeletonization of the greater curvature to resect the gastroepiploic arcade with the adjacent lymph nodes, following again the “10-cm rule” according to the vertically running vessels of the greater omentum in relation to the site of the primary tumour including en bloc the omentum into the specimen and dissection of the lymph nodes over the pancreatic head for tumours of the right transverse colon including the hepatic flexure was performed, as described previously (1).

The examined lymph node regions (ILR, GLR) together with central vascular ligation (CVL) were marked with sutures of different colour (Figs. 1, 2 and 3: blue for CVL, white for GLR and green for ILR), and these were examined thoroughly and independently by two pathologists (Fig. 4).

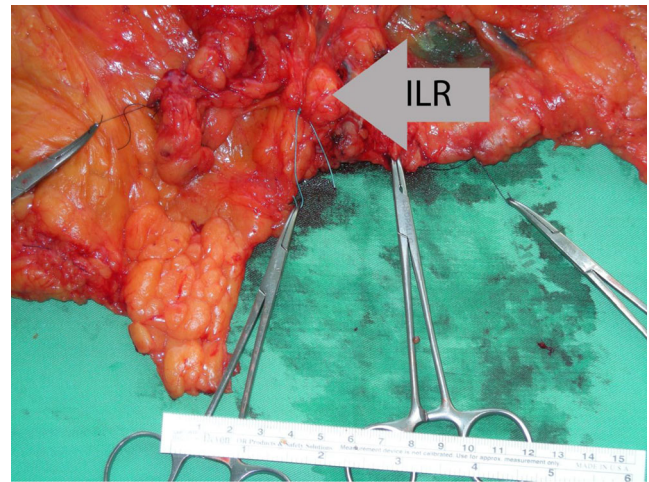
Complications have been classified in surgical and non-surgical complications.

#### Histopathological staging

The detailed TNM classification of all patients is demonstrated in Table 1. Twenty-two patients had a carcinoma of moderate differentiation (G2) and in 24 patients a poorly differentiated carcinoma (G3) was diagnosed. Thirty six patients underwent a R0 resection, one patient R1 resection and eight patients palliative resection due to synchronous distal metastases (liver metastasis,  $n=1$ ; peritoneal carcinomatosis,  $n=7$ ). The patient with a R1-resection had a carcinoma of the transverse colon with infiltration of the head of the pancreas (Fig. 5) and underwent an extended right hemicolecotomy



**Fig. 1** Front side of specimen after subtotal colectomy and overview of the marked lymph node regions (CVL central vascular ligation, ILR infrapancreatic lymph node region, GLR lymph node region around right gastroepiploic artery)



**Fig. 2** Marking of the lymph node regions. Green suture: ILR

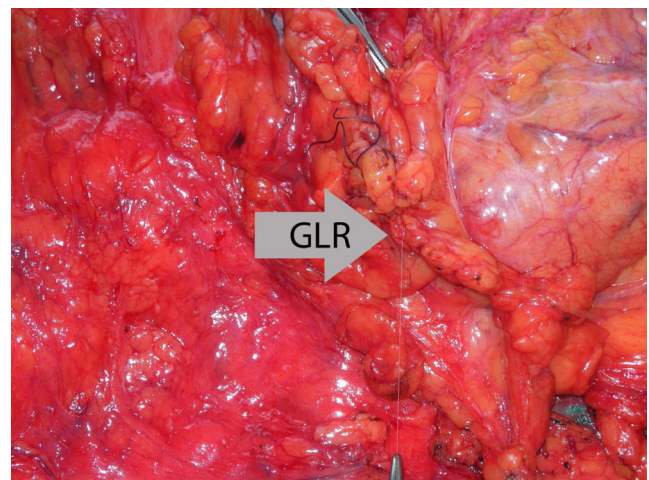
and Whipple procedure and resection of the junction of the splenic and superior mesenteric vein followed by vascular reconstruction, and finally with microscopic residuals at the portal vein.

Furthermore, we analyzed lymph node yield, lymph node ratio (LNR), the specific lymph node manifestation according to the intraoperative marking of the lymph node regions (CVL, ILR, and GLR), site of tumour, extend of bowel resection, morbidity, and mortality, clinical and postoperative outcome.

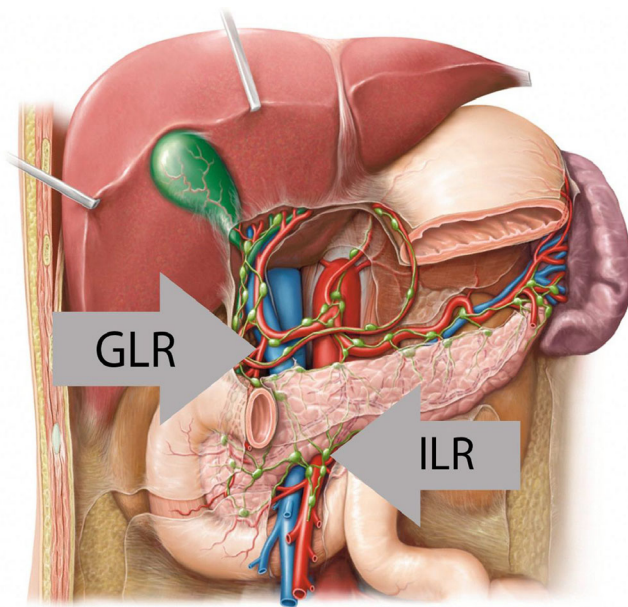
#### Results

##### Study population, site of carcinoma, tumour characteristics

Between May 2010 and January 2013, 45 patients (women,  $n=18$ ; men,  $n=27$ ) with a diagnosis of carcinoma of the



**Fig. 3** Marking of the lymph node regions. White suture: GLR



**Fig. 4** Overview and ILR, GLR

transverse colon, hepatic or splenic flexure were referred for surgical evaluation to the Department of Surgery, University Hospital of Erlangen. The patients' physical status was assessed according to the American Society of Anesthesiologists (ASA) classification (Table 1).

In 26 patients (58 %), a carcinoma of the transverse colon was detected, 15 patients (36 %) had a diagnosis of a carcinoma of the hepatic flexure and four patients (16 %) of the splenic flexure. In one patient, there was a carcinoma of the transverse colon and the hepatic flexure as well. Two patients underwent surgery as emergencies and underwent the same surgical procedure as elective cases. The vast majority of the patients ( $n=43$ ) underwent elective surgical treatment.



**Fig. 5** Computed tomography scan of patient with carcinoma of the transverse colon with infiltration of the head of pancreas, underwent subtotal colectomy and Whipple procedure

#### Lymph node yield/Examination of the different lymph node regions

The median lymph node yield was 40 (range: 19–125). Twenty-four patients (52 %) had a positive lymph node status. Occurrence of lymph node metastasis in the ILR region was registered in five of 45 patients (11 % or 20 % of patients with nodal positive status) and in the GLR in four patients (9 %, 16 % of patients with nodal positive status). In the rest of the patients with nodal positive carcinoma ( $n=18$ ), lymph node metastases were registered only in the pericolic lymph node region. Overall, in three patients (two with carcinoma of the transverse colon and one with carcinoma of the hepatic flexure), we found metastasis in distant lymph nodes, without involvement of the pericolic lymph nodes.

In two patients with nodal positive carcinoma, lymph node metastases were only present in the main nodes area (CVL) and one patient with nodal positive carcinoma of the transverse colon had lymph node metastases in the ILR.

The mean LNR in patients with nodal positive status and carcinomas in UICC stadium III ( $n=16$ ) was 0.085 (range: 0.018–0.25). The mean LNR in all patients with nodal positive carcinomas (UICC stadium III and IV) was 0.102 (range: 0.018–0.5).

#### Analysis of the patient with positive lymph node status in ILR and GLR

Overall, eight patients underwent surgery for either carcinoma of the transverse colon or of the hepatic flexure had lymph node metastases along ILR and GLR. All patients with involvement of both regions have been classified under UICC stage IV, according to the latest TNM classification (17), which considers the extramesocolic lymph node manifestation as metastatic disease. However, only three of them had synchronous peritoneal metastasis or distant metastasis in other sites (Table 1). Involvement of both regions was found in one patient with subtotal colectomy for carcinoma of the transverse colon. In patients with carcinoma of the transverse colon ( $n=26$ ) lymph node metastases were seen in both regions (ILR and GLR) in one case, only in ILR in three cases and only in GLR in two cases. In patients with carcinoma of the hepatic flexure ( $n=15$ ) lymph node metastases in ILR were identified in one case and in GLR in one patient. In patients undergoing surgery for carcinoma of the splenic flexure lymph node metastases were seen neither in ILR nor in GLR.

#### Postoperative complications, outcome

The postoperative outcome was uneventful in 36 patients (80 %). Postoperative complications occurred in nine patients (Table 2). Surgical complications were seen in six patients. One patient developed an anastomotic leakage needing

**Table 2** Complications in 45 patients

	Patients (n)	Percentage (%)
None	36	80
Surgical complications <sup>a</sup>		
Anastomotic leakage	1	2
Sepsis	1	2
Colon necrosis	1	2
Lymph fistula	1	2
Impairment of micturition	1	2
Hematoma	1	2
Wound infection	2	4
Nonsurgical complications		
Cardiological	3	7
CVC infection	1	2
Renal failure	2	4
In-hospital mortality	1	2

CVC central venous catheter

<sup>a</sup>More complications in one patient possible

reoperation. Furthermore, minor surgical complications, such as hematoma and lymph fistula, occurred in three patients and have been treated conservatively. In-hospital mortality was 2 % ( $n=1$ ). This patient presented with an advanced transverse colon carcinoma with infiltration of the pancreatic head, needing Whipple procedure and died after discharge but related to the surgical procedure after 2 months. There was no postoperative pancreatitis.

## Discussion

Colorectal cancer is one of the most common malignant tumours worldwide [18–21]. This represents an enormous challenge and creates huge interest, especially with respect to the oncologically correct surgical treatment [1–4].

In recent years, most of the published studies focused mainly on the treatment of rectal carcinoma with standardisation of the surgical technique and the interdisciplinary approach of the disease. This led to the introduction and acceptance of an interdisciplinary therapeutic algorithm including TME and neoadjuvant chemoradiation in locally advanced cases, as state of art [5–9, 22–25].

This standardized process led to a change of the trend in favour of rectal carcinoma in terms of local recurrence and 5-year survival rates compared to colon, although adjuvant chemotherapy, including irinotecan, oxaliplatin and biologicals, was probably more frequently applied in colon cancer patients [26–28].

It has been confirmed that CME produces superior quality of specimens compared to conventional surgery [3, 4]. CME

represents also the surgical background for the maximal lymph node harvesting, an important marker for quality as far as the surgical outcome is concerned [3, 4, 10–14]. Similarly, the application of adjuvant chemotherapy in patients with nodal positive status plays a major role and significantly improves outcomes [27]. However, it cannot replace deficits in cases of low quality surgery. Therefore, the combination of high quality surgery in terms of CME with extensive lymph node dissection and the significant benefits coming from the adjuvant chemotherapy represents a multidisciplinary approach in order to improve outcomes in patients suffering from colon cancer, especially in these with the diagnosis of UICC stage III disease.

Although several reports postulated that a radical lymph node excision could lead to a more complicated course with increased morbidity, it has been recently reported that an excellent oncologic surgical outcome can be performed without significant increase of overall morbidity or mortality rates over the last 20 years [2]. Even the increased morbidity in terms of anastomotic leakage and need of reoperation — registered in the patients' collective over the years 2000 to 2004 as published in the study of Weber et al. [2] — has been an incidental finding, as the morbidity and rate of anastomotic leakages has been significantly decreased in the years 2005 to 2010 (19.9 % and 1.8 %, respectively) [2]. Furthermore, the fact that all patients regardless of emergency status, progressive finding, such as T4 tumours, have been included in the analysis cannot be underestimated and could be an important factor for these results. Additionally, it is important to mark the transparency of the results of the performed studies, as most of clinical trials have strict exclusion criteria [1–4].

In this context, apart from the quality of plane preservation, the extent of lymph node dissection also matters. Until now, mainly the number of regional lymph node and central tie were most frequently discussed. However, in cancer of the transverse colon including flexures, the “third dimension,” which is along the inferior pancreas and the gastroepiploic arcade, has not been consequently considered. There is only some data on the nodes over the pancreatic head [1] and on those along the greater curvature of the stomach in cases of right sided colon carcinomas [15]. In patients with a nodal positive carcinoma of the transverse colon and of both flexures, the involvement of lymph node metastasis in the ILR and across the gastroepiploic arcade and in the lymph node region of the right gastroepiploic artery (GLR) was observed in 20 % overall. In the presence of infiltration of the greater omentum, in particular, infrapancreatic metastases have been more frequent. Considering the embryologic background, there are vascular connections between both colonic flexures and greater omentum and uncinate process of the pancreas, which explain the occurrence of metastases in these regions.

The metastatic route in ILR results from the lymphatic drainage to lymph nodes along the arterial supply via

collaterals from the left-sided branches of the middle colic artery towards the left pancreas to the Rami pancreatici and Arteria (A.) pancreatica transversa und inf. arising from the inferior gastroduodenal artery. This is the connection between these vessels and the left mesocolon, which has not been described before. As far as the direct lymphatic route in GLR is concerned, this occurs over direct connections between branches of the right gastroepiploic artery and omentum vessels. This is the anatomic background of these direct lymphatic drainage ways, which can lead to lymph node metastasis of transverse colon carcinomas in ILR and GLR. Furthermore and according to previous reports [1], in about 5 % of carcinomas of the hepatic flexure, metastases can be found over the pancreatic head and this could be the result through a potential anastomosis between the A. pancreatica magna and A. pancreatica transversa in the ILR. Additionally in cancer of the transverse colon and the splenic flexure, lymphatic metastasis could be observed along the greater curvature of the stomach and the distal (left) infrapancreatic region [1].

Although there has been, until now, no valid data in the literature on this subject, we performed radical oncologic surgery, as previously described, including GLR and ILR with intraoperative marking of these lymph node areas for more than 20 years, as described above.

In our series, we were able to confirm first that these lymph nodes could have a significant oncologic impact, because lymph node metastases could be detected in the ILR and in GLR in 20 % and 12.5 % of the patients with a nodal positive carcinoma, respectively.

We also have to emphasize that three patients of our series had metastasis in distant lymph node regions (GLR, CVL) without involvement of the pericolic lymph node area.

These lymph node metastasis routes have not been systematically evaluated in the literature; however, our results deliver strong arguments to include these lymph node regions into the lymph node dissection in case of carcinoma of the transverse colon and both flexures.

Most of these patients suffered from a carcinoma of the transverse colon ( $n=6$ ). However, there were two patients with carcinoma of the hepatic flexure which showed metastases in both lymph node regions (one patient with lymph node metastasis in ILR and one patient in GLR). This patient had also lymph node metastases in the lymph node area over the pancreatic head and our hypothesis is that there is a metastatic route over the right gastroepiploic artery to A. pancreatica transversa and Rami pancreatici.

As far as the dogmatic statement is concerned — that a radical excision with extensive lymph node dissection necessarily leads to an increased morbidity and mortality, we could assert that our standardized technique did not induce any significant disadvantage for the patients and their postoperative course [2]. Of course — and in the verge of extended

lymph node dissection — there could be an increased morbidity in cases of: surgical treatment after operative exploration because of the adhesions, previous pancreatitis or in cases of presence of chronic pancreatitis and/or pseudocysts and low experience in terms of CME and/or surgical–anatomic knowledge of the sensitive region over the pancreas head and the infrapancreatic region. These regions are very well vascularised, and the risk of an intraoperative or postoperative bleeding is very high, if the anatomic characteristics are not taken into consideration [1]. However, the risk for both morbidity and mortality was very low, and 80 % of the patients in the present series had an uneventful course. There was the need for reoperation in one case of anastomotic leakage, and all other complications that occurred could be managed either conservatively or interventionally. Furthermore, mortality is not increased. On the other hand and in order to avoid the high risk of an increased morbidity, in terms of postoperative pancreatitis, we discourage the dissection of the nodes along pancreas, if there are firm fibrous fixations due to earlier pancreatitis or in presence of a chronic pancreatitis.

Limitations of the present study are the absence of a long follow-up and the impact of this surgical technique on the survival and disease-free rates in these patients. Furthermore this study does not have the advantages of a randomized clinical trial. Nevertheless, the data reported included all patients that underwent elective and emergency surgery. Another limitation is that this study was performed in a single institution and the results obtained might not be comparable to those in other centers. Unicentral studies, however, have the advantage of reducing the number of possible differences in surgical technique.

These metastatic routes are not considered as regional lymph node stations in the current UICC classification [17]. Metastasis in these regions are until now considered as distant metastasis. If these metastatic regions were considered as regional lymph node regions, four patients of our collective were classified under UICC stadium III according UICC classification [17]. Our results based on embryologic and anatomical considerations which identify these nodes as regional lymph nodes should be considered when the actual UICC staging system of colon cancer will be reconsidered. Finally, these findings need to be reevaluated in other centers, too.

## Conclusion

Through this study, we were able to demonstrate this novel, not previously described metastatic route of the transverse colon carcinomas to the ILR and the region along the gastroepiploic arcade. The incidence of the lymph node metastasis in these regions in the present series was 20 % and 12.5 %, respectively, in patients with a nodal positive

carcinoma. Furthermore, we showed that the occurrence of metastasis in these lymph nodes is not obligatory correlated with peritoneal dissemination or other distant metastasis. Even more, these lymph node stations may represent regional nodes and its involvement not necessarily distant metastases, as they are now staged in the actual TNM staging system. Therefore, the excision of the infrapancreatic lymph nodes and the gastroepiploic arcade should be included into radical lymph node dissection of transverse colon cancer.

Progress in oncology and even more in surgical oncology is a stepwise procedure. Like a mosaic, each little stone contributes to improvement.

## References

- Hohenberger W, Weber K, Matzel K et al (2009) Standardized surgery for colonic cancer: complete mesocolic excision and central ligation—technical notes and outcome. *Color Dis* 11:354–364
- Weber K, Merkel S, Perrakis A, Hohenberger W (2013) Is there a disadvantage to radical lymph node dissection in colon cancer? *Int J Color Dis* 28(2):217–226
- West NP, Hohenberger W, Weber K et al (2010) Complete mesocolic excision with central vascular ligation produces an oncologically superior specimen compared with standard surgery for carcinoma of the colon. *J Clin Oncol* 28:272–278
- West NP, Kobayashi H, Takahashi K et al (2012) Understanding optimal colonic cancer surgery: comparison of Japanese D3 resection and European complete mesocolic excision with central vascular ligation. *J Clin Oncol* 30(15):1763–1769
- Heald RJ, Husband EM, Ryall RDH (1982) The mesorectum in rectal cancer surgery — the clue to pelvic recurrence? *Br J Surg* 69:613–616
- Heald RJ, Ryall RD (1986) Recurrence and survival after total mesorectal excision for rectal cancer. *Lancet* 327:1479–1482
- Cecil TD, Sexton R, Moran BJ, Heald RJ (2004) Total mesorectal excision results in low local recurrence rates in lymph node positive rectal cancer. *Dis Colon Rectum* 47:1145–1150
- Nagtegaal ID, van de Velde CJH, van der Worp E et al (2002) Macroscopic evaluation of rectal cancer resection specimen: clinical significance of the pathologist in quality control. *J Clin Oncol* 20:1729–1734
- Quirke P, Steele R, Monson J et al (2009) Effect of the plane of surgery achieved on local recurrence in patients with operable rectal cancer: a prospective study using data from the MRC CR07 and NCIC-CTG CO16 randomised clinical trial. *Lancet* 373:821–828
- Chen SL, Bilchik AJ (2006) More extensive nodal dissection improves survival for stages I to III of colon cancer: a population-based study. *Ann Surg* 244:602–610
- Johnson PM, Porter GA, Ricciardi R, Baxter NN (2006) Increasing negative lymph node count is independently associated with improved long-term survival in stage IIIB and IIIC colon cancer. *J Clin Oncol* 24:3570–3575
- Schumacher P, Dineen S, Barnett C Jr, Fleming J, Anthony T (2007) The metastatic lymph node ratio predicts survival in colon cancer. *Am J Surg* 194:827–832
- Le Voyer TE, Sigurdson ER, Hanlon AL et al (2003) Colon cancer survival is associated with increasing number of lymph nodes analyzed: a secondary survey of intergroup trial INT-0089. *J Clin Oncol* 21:2912–2919
- Mammen JM, James LE, Molloy M, Williams A et al (2007) The relationship of lymph node dissection and colon cancer survival in the Veterans Affairs Central Cancer Registry. *Am J Surg* 194:349–354
- Toyota S, Ohta H, Anazawa S (1995) Rationale for extent of lymph node dissection for right colon cancer. *Dis Colon Rectum* 38:705–711
- Jass JR, Sobin LH (1989) Histological classification of tumours, 2nd ed. WHO international histological classification of tumours. Springer, Berlin
- Sobin LH, Gospodarowicz M, Wittekind C (2009) UICC TNM classification of malignant tumors, 7th edn. John Wiley & Sons, New York
- Cancer Res UK. Cancer Stats. <http://info.cancerresearchuk.org/cancerstats/types/bowel/>
- American Cancer Society: Cancer Facts and Figures (2009) [http://www.cancer.org/docroot/STT/STT\\_0.asp](http://www.cancer.org/docroot/STT/STT_0.asp)
- Koyama Y, Kotake K (1997) Overview of colorectal cancer in Japan: report from the Registry of the Japanese Society for Cancer of the Colon and Rectum. *Dis Colon Rectum* 40(suppl):S2–S9
- International Agency for Research on Cancer, World Health Organization: GLOBOCAN (2008) Cancer Incidence and Mortality Worldwide in 2008. <http://globocan.iarc.fr/>
- Heald RJ (1988) The ‘Holy Plane’ of rectal surgery. *J R Soc Med* 81:503–508
- Sauer R, Becker H, Hohenberger W et al (2004) Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 351:1731–1740
- Bosset JF, Collette L, Calais G et al (2006) Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med* 355:1114–1123
- Folkesson J, Birgisson H, Pahlman L et al (2005) Swedish Rectal Cancer Trial: long lasting benefits from radiotherapy on survival and local recurrence rate. *J Clin Oncol* 23:5644–5650
- Taal BG, Van Tinteren H, Zoetmulder FA (2001) NACCP group Adjuvant 5FU plus levamisole in colonic or rectal cancer: improved survival in stage II and III. *Br J Cancer* 85:1437–1443
- André T, Boni C, Mounedji-Boudiaf L et al (2004) Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) Investigators Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med* 350:2343–2351
- Link KH, Kornmann M, Staib L et al (2005) Study Group Oncology of Gastrointestinal Tumors Increase of survival benefit in advanced resectable colon cancer by extent of adjuvant treatment: results of a randomized trial comparing modulation of 5-FU + levamisole with folinic acid or with interferon-alpha. *Ann Surg* 242:178–187