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Actual standards and controversies on operative technique and lymph-node dissection in colorectal cancer

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Abstract *Background:* Radical lymphadenectomy for colorectal cancer according to its arterial supply seems to remove potentially metastatic lymph nodes and highlights the impact on prognosis. *Standards and controversies:* Systematic lymph-node dissection in colorectal cancer requires knowledge of normal anatomy of lymphatic drainage and spreading of lymph-node metastases. Oncological standards of curative surgery for colorectal cancer include en bloc resection, no-touch isolation technique, primary ligation of the vessels and systematic lymphadenectomy. In rectal cancer, total mesorectal excision and irrigation of the rectal stump is mandatory. Potential improvements in prognosis achieved by extended lymph-node dissection have to compete with procedure-related morbidity. High-tie ligation of the inferior mesenteric artery is a controversial issue. Prediction of prognosis is essential for planning a treatment schedule for patients. *Conclusions:* At present, clinicopathological stage is the single most reliable factor in prediction of outcome. New encouraging methods for detecting micrometastases of lymph nodes and new surgical technologies such as immune corrective surgery are challenging and have to be critically assessed. The results of laparoscopic surgery for the cure of colorectal cancer have to be proven within prospective randomised trials.

Key words Colorectal cancer · Lymph-node dissection · Oncological surgery · Survival · Recurrence

Introduction

Prognosis and treatment of colorectal cancer, as reflected in the TNM classification [1], Dukes classification [2] Astler-Coller staging system [3] and UICC/AJCC classification [1, 4], are mainly determined by the presence of lymph-node metastases in the surgically removed specimen. Both detection and histopathological examination of the largest possible number of lymph nodes are mandatory for correct staging, therapeutic decisions, including adjuvant therapeutic options, and prognosis in patients with colorectal cancer. At present, histopathological staging still remains the most valuable prognostic factor of colorectal malignancy [5–9]. Simultaneously, clinical studies suggest that, in colorectal malignancy, the number of positive lymph nodes combined with the mural penetration are the most valuable predictive factors of survival. Other factors, such as gross appearance, lymphatic and vascular invasion, age, gender, ploidy status or apoptotic index, are still controversially discussed. As prospective randomised trials that evaluate the definite role of radical lymph-node dissection for colorectal cancer are still missing, it was the aim of the current review to describe anatomical and historical aspects of lymph-node dissection, to describe the policy of surgery for the cure of colorectal neoplasia including systematic lymph-node dissection and to critically assess several technical aspects of colorectal surgery for cancer which may have a bearing, in particular, on recurrence and survival.

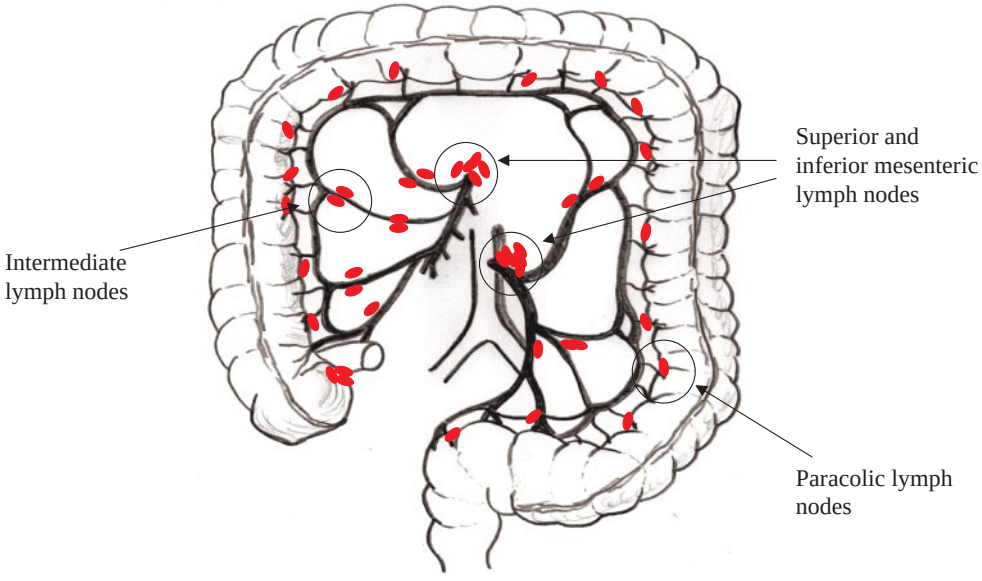

Fig. 1 Lymphatic drainage of the colon

Basic principles of lymph-node dissection in colorectal cancer

Anatomy of lymphatic drainage of the colon and rectum

Similar to venous drainage, lymphatic drainage of the colon and rectum basically follows its arterial supply (Figs. 1, 2). Consequently, variations of the arterial supply have an important impact on lymphatic drainage [10]. Generally, three lymphatic drainage pathways can be differentiated: (1) lymphatic drainage of the right colon and proximal transverse colon following the arterial supply of the superior mesenteric artery and vein; (2) lymphatic drainage of the left colon and the upper two-thirds of the rectum along the inferior mesenteric artery and vein; and (3) lymphatic drainage from the lower two-thirds of the rectum occurs cephalad, along the superior rectal artery and the inferior mesenteric artery and, laterally, along the middle rectal vessels to the internal iliac lymph nodes. Studies using lymphoscintigraphy fail to demonstrate communications between inferior mesenteric and internal iliac lymphatics [11]. In the anal canal, the dentate line represents the essential landmark for two different systems of lymphatic drainage: above, to the inferior mesenteric nodes and, below, along the inferior rectal lymphatics to the superficial inguinal nodes, or less frequently, along the inferior rectal artery.

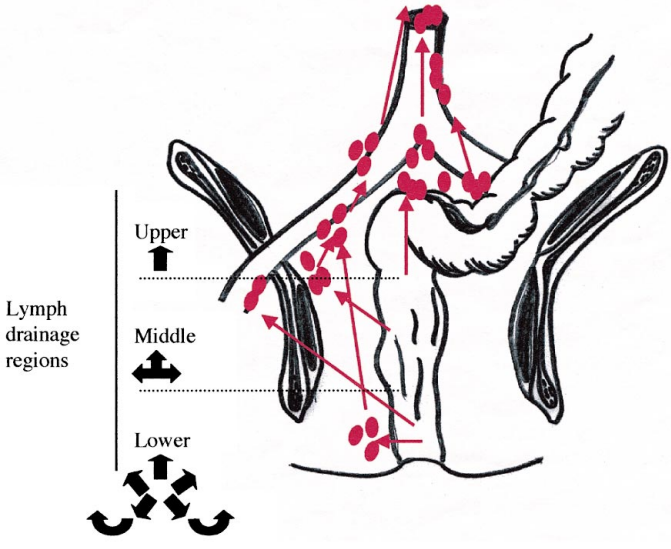

Fig. 2 Lymphatic drainage of the rectum

Spreading of lymph-node metastases

According to the recommendations of the *International Union Against Cancer* (UICC), lymph-node metastases are defined as histologically detectable spread of tumour cells with corresponding tissue reaction. In general, macrometastases can be differentiated from micrometastases (2 mm or smaller in size), whereas, by definition, tissue reaction must also be demonstrated in micrometastases [12–14]. Lymph-node metastases can arise either continuously or discontinuously. In case of continuous spread of tumour cells, the pathway follows lymphatic fissures and lymphatic capillaries to the corresponding lymphatic stations next to the bowel wall (epicolic or perirectal lymph nodes). More frequently, lymph-node metastases arise sequentially along epicolic or pericolic lymph nodes to the intermediate lymph nodes (right colic artery, middle colic artery, left colic artery, sigmoidal arteries) and, finally, to the central lymph nodes lo-

cated at the origin of these branches (superior mesenteric artery, inferior mesenteric artery).

In less than 5%, "skip metastases" can occur, if metastases arise in intermediate lymph nodes but not in epicolic and pericolic lymph nodes [10]. In general, spreading of lymph-node metastases follows normal lymphatic drainage of the colonic or rectal segment. Lehnert and Herfarth emphasised that exceptions of lymph-node metastases can occur due to collateralisation [10]. In rectal cancer, spread of tumour cells can be detected in the mesorectum, arising discontinuously and potentially without lymph-node tissue [14]; these are defined as lymph-node metastases if the diameter is 3 mm or larger, whereas smaller infiltrations of tumour cells are defined as "satellites" [12–14]. Specifically in rectal cancer, Scott and colleagues could demonstrate that spread of tumour cells occurs in the distal mesorectum in up to 20% of rectal cancers, both by direct and lymphatic extension, and permeation of the surrounding mesorectum occurs both radially and longitudinally [15]. In an additional series, Omi and colleagues investigated 123 patients with rectal cancer and reported that the frequency of lymph-node metastases was significantly increased in cases of lower rectal cancer compared with that of upper rectal cancer [16]. Other series reported the role of peritoneal reflection. When carcinomas were located in the lower rectum, lymphatic spread of cancer might not occur exclusively along the superior rectal and inferior mesenteric vessels to the para-aortic lymph nodes, but also along the middle rectal to internal and common iliac vessels [17, 18]. Heald and colleagues have described discontinuous mesorectal deposits up to 4 cm below the main tumour mass [19]. Both experimental and clinical studies highlight that the role of spread of lymph-node metastases is essential for radical surgery for the cure of colorectal cancer, and total mesorectal excision (TME) is mandatory in rectal cancer, particularly in patients with carcinomas located in the middle and lower third of the rectum [15, 18–21].

Detection of lymph-node metastases

Following the report by Lehnert and Herfarth [10], we know that the detection of lymph-node metastases depends on several variables: anatomical variations, extent of surgical resection and pathological processing. As it is known that lymph-node metastasis is one of the most important prognostic factors in colorectal carcinoma, an adequate yield of lymph nodes for detection of lymph-node metastases is essential before being able to determine the stage or make any decision about adjuvant therapeutic modality. Theoretically, sampling the entire pericolic or perirectal fat would be the most accurate method for total lymph-node examination. Therefore, the fat-clearing technique is a more practical technique [22–24]. Precise processing of lymph nodes in surgically removed specimens shows that 80% of lymph-node metastases were found in lymph nodes smaller than 5 mm in diameter, whereas, in macroscopically enlarged lymph nodes, inflammatory components were more common [10].

Koren and colleagues have recently introduced an easy, rapid and inexpensive method to detect minute lymph nodes in specimens from those with colorectal cancer [25]. The authors introduced the LNRS method (lymph-node-revealing solution) and showed that the stage of the disease could be determined more accurately using this method [25]. They proposed to use the LNRS method in routine pathological work-up of colorectal cancer specimens [25]. However, among patients with no histopathologically detectable lymph-node metastases, 20–30% die from a local tumour relapse or distant metastases. This might be explained by an early dissemination of tumour cells into lymph nodes that cannot be detected using conventional pathological work-up techniques. Consequently, the application of serial sectioning methods could be an important benefit. Gusterson reported that up to 20% of cases diagnosed as negative for lymph-node metastases on routine section work-up can be shown to contain micrometastases after serial sectioning [26]. Furthermore, the prognostic relevance of occult tumour cells in lymph nodes has still not really been elucidated. Following the results of our Division of Surgical Research, occult tumour cells might increase the risk of local or distant recurrences, but did not significantly influence patients' prognosis at all [27]. Using immunhistochemical methods – tumour-negative by conventional pathological examination (pN0) – analysing paraffin blocks of lymph nodes from 49 patients with colorectal cancer (UICC stages I–III) after curative resection, occult tumour cells were detected in 26.5% (13/49). There was a correlation demonstrable between the detection rate and N category, tumour stage and histological differentiation. Additionally, 33% of patients with stages I and II and with occult tumour cells in lymph nodes (N0+) developed local and/or distant recurrence in contrast with 12% of patients with no tumour cells (N0–) [27].

Several investigators have tried to study the significance of lymph-node micrometastases in Dukes stages A and B or UICC stage-II (with no lymph-node metastases) colorectal cancer and to identify patients who are at high risk for recurrence. Using a carcinoembryonic antigen (CEA)-specific nested reverse-transcriptase polymerase chain reaction in 192 lymph nodes from 26 consecutive patients, Liefers and colleagues detected micrometastases in 14 of 26 patients (54%) with stage-II colorectal cancer [28]. The adjusted 5-year survival rate (including only cancer-related deaths) was 50% in this group (14 of 26; with micrometastases), whereas the survival rate was 91% in the other group of patients (12 of 26; with no micrometastases) [28]. Both the adjusted survival rates and the observed 5-year survival rates (36% in patients with micrometastases vs 75% in patients with no micrometastases) were significantly higher in patients with no micrometastases and,

therefore, the authors concluded that molecular detection of micrometastases is a prognostic tool in stage-II colorectal cancer [28]. Conversely, Öberg and colleagues examined archival specimens from 147 patients who had curative surgery for colorectal cancer Dukes stages A and B using an anticytokeratin antibody and identified lymph-node micrometastases in 32% (47 of 147 patients) [29]. However, no statistically significant differences were documented according to micrometastases when the results were analysed with respect to Dukes stage or survival time [29]. In contrast to Liefers and colleagues [28], the authors concluded that lymph-node micrometastases are not a useful prognostic marker in lymph-node-negative patients and do not imply different strategies for adjuvant therapy or follow-up [29].

Detection of lymph-node metastases and exact determination of pN status are essential for prediction of prognosis and planning therapeutic modalities. In colorectal cancer, it is important to estimate the number of lymph nodes involved by the tumour in relation to the total number of lymph nodes examined (minimum 12 nodes) in the resected specimen [12, 30]. Concerning patients' prognosis, 5-year survival rate decreases from 70 to 80% in Dukes A + B stages to 30 to 40% in Dukes C stage [12, 30]. In an additional series, Sitzler and colleagues showed that lymph-node positivity, the number of lymph nodes involved, lymphatic vessel invasion, and venous and perineural invasion were significantly increased with increasing depth of tumour penetration through the bowel wall [31].

The significance of the mean number of lymph nodes detected by the pathologists was outlined by Goldstein and colleagues [32]. They reported that the mean number of lymph nodes recovered per specimen of pT3 colorectal cancer and the incidence of detected lymph-node metastases increased over a 41-year period (1955–1995) [32]. Interestingly, the highest proportion of patients with detected lymph-node metastases occurred in the group in which 17–20 lymph nodes were recovered per specimen, whereas specimens with more than 20 lymph nodes did not show a higher proportion of detected lymph-node metastases than specimens with 17–20 lymph nodes [32]. Therefore, the authors recommended that the pathologists should retrieve all the lymph nodes that can be recovered, but at least 17 lymph nodes to ensure accurate documentation of potential nodal metastases in colorectal cancer specimens [32].

Significance of operative technique and lymph-node dissection in colorectal cancer

Historic perspectives of curative surgery for colorectal cancer

Since the 1880s, essential steps have been taken in the surgical treatment of colorectal cancer. Following the publications of Halsted in 1894 [33] and Moynihan in 1908 [34], the standard surgical treatment for colorectal cancer was defined as en-bloc resection of the tumour-bearing segment with central ligation of its vessels and included resection of the mesenterium which contains the corresponding lymph nodes. In 1908, the pathological studies of Miles on lymphatic involvement introduced abdominoperineal excision of the rectum as the sole curative procedure in the treatment of rectal cancer [35]. In 1932, Dukes published the first staging system for rectal cancer which referred to mural penetration and lymph-node metastases [36]. Since that time, the Dukes classification has been modified and has also been adopted for colon cancer. An additional oncological standard was described by Turnbull and colleagues in 1967 [37]; the no-touch isolation technique emphasised the importance of ligation of the blood supply prior to attempted mobilisation of the tumour. An improvement of survival was particularly noted for Dukes C carcinomas [37]. Concerning systematic lymph-node dissection, radical lymphadenectomy was compared with conventional lymphadenectomy in several studies, but none of them was randomised [38–43], although two series showed a statistically significant increase of the 5-year survival rate after radical lymphadenectomy [40, 42]. In 1986, Heald showed that TME was mandatory in rectal cancer and oncological results were superior to partial mesorectal excision (Fig. 3) [44]. Finally, in 1987, the classification system of colorectal cancer was unified by the UICC

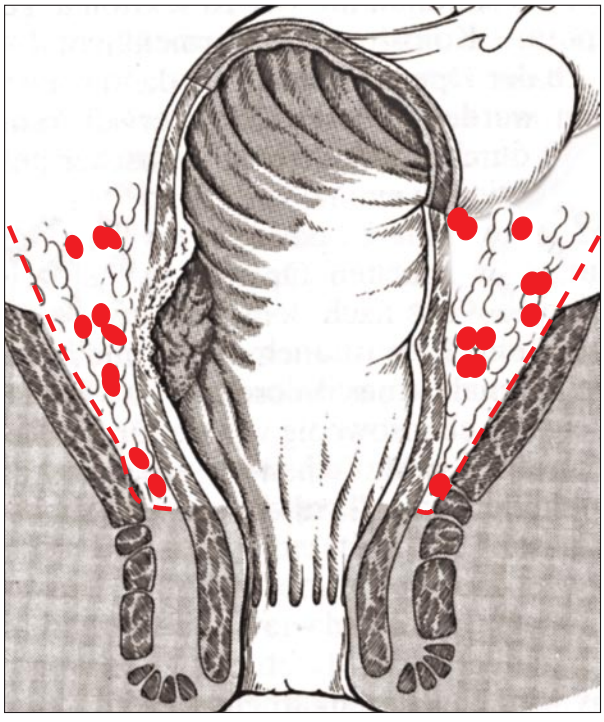

Fig. 3 TME (total mesorectal excision)

and by the AJCC (American Joint Committee on Cancer) based on the TNM staging system [1, 4].

Surgical standards for the cure of colon cancer

Surgical standards for the treatment of colon cancer generally include radical resection of the tumour-bearing colon with central ligation of its vessels [45, 46]. The lymphatic dissection determines the extent of colonic resection; with curative intent, standard procedures are right hemicolectomy, transverse colectomy, left hemicolectomy, sigmoid resection and anterior resection. The ligation close to the origin of the corresponding segmental arteries is widely accepted for cancer of the right and transverse colon (ileocolic artery, right colic artery, middle colic artery) and for cancer of the left colon (left colic artery, sigmoidal arteries, inferior mesenteric artery). Carcinomas located in between two drainage areas make extended hemicolectomies or subtotal colectomy with systematic dissection of two lymphatic drainage areas mandatory. Other indications for subtotal colectomy include associated polyps (not removable by colonoscopy), synchronous carcinomas in different segments of the colon and young age of the patient (<50 years) combined with positive family history. In case of sigmoid cancer, the inferior mesenteric artery is ligated at its origin from the aorta and the inferior mesenteric vein at the level of the duodenum and pancreas. Surgeons who advocate the no-touch isolation technique ligate the lymphovascular structures prior to any mobilisation. Therefore, an incision is made in the root of the mesentery and the trunks of the vessels are identified, divided and ligated as initial manoeuvre. The major concern with this policy is the potential need to deal with the structures such as the duodenum, ureter and gonadal vessels without the benefit of adequate exposure. Wiggers and colleagues did not find any statistically significant advantage regarding survival with the no-touch technique [47]. In their series, 236 patients were randomised to either the no-touch or the conventional technique. The 5-year survival rates did not show any statistically significant differences (60% vs 56%, respectively) [47].

Exceptions from curative resections can be necessary in cases of metastatic disease (palliative segmental resection with local lymphadenectomy) or emergency surgery for colonic obstruction.

Long-term results of the German Colorectal Cancer Study Group demonstrated clearly the importance of principles of radical surgery for colon cancer and gave evidence for the outstanding relevance of surgery for the prognosis of colon cancer [48]. This prospective multicentre study reported on 1157 patients who underwent surgery for colon cancer. Multivariate analysis using the logistic regression model identified R-classification, stage, institution and timing of surgery as independent prognostic factors in terms of survival [48]. Particularly in R0 resected patients, the incidence of local recurrence was the strongest prognostic factor [48]. Furthermore, the study demonstrated an essential variability in local recurrence and survival rates among the participating institutions [48]. Therefore, the essential role of the surgeon has to be recognised, and standardised operative techniques in colorectal cancer surgery, including adequate lymph-node dissection, are necessary. According to the results of the German Colorectal Cancer Study Group [48], the surgeon is an important variable influencing oncological outcome, including local recurrence and survival, and prognosis for the patient.

Surgical standards for the cure of rectal cancer

Radical surgery remains the primary treatment in rectal cancer and prognosis primarily depends on the extent of tumour at the time of diagnosis. As diagnostic assessment is performed more and more precisely and surgical techniques have been clearly improved within the last decade, the rate of curative resections and sphincter-saving procedures for rectal cancer have been significantly increased and mortality rates have been decreased [49–52]. Concerning surgical treatment, three requirements have to be fulfilled: adequate locoregional clearance, acceptable morbidity and acceptable functional results – in the case of malignancy, the first requirement is the most important. In general, there are two options relating to rectal cancer: sphincter-saving procedures (low anterior resection, intersphincteric resection) and abdominoperineal excision of the rectum. A few patients with low-risk carcinomas (pT1) confined to the rectal wall are amenable for local excision [53]. In case of low-risk cancer of the lower third of the rectum (pT1), lymph-node metastases occur in 3% [54] and 5-year survival after local excision in these patients is approximately 90% [55]. Modern technology affording access to the upper and middle rectum, e.g. transanal endoscopic microsurgery [56, 57], may increase the scope of local excision, but the oncological criteria of case selection (low-risk, T1, free resection margins) must still be applied [52, 53].

Analysis of the literature shows that there are many issues of concern involved in radical surgery for the cure of rectal cancer, including high or low ligation of the inferior mesenteric artery, TME and extended lymphadenectomy [58].

Ligation of the inferior mesenteric artery may be performed at a point just below the take off of the left colic artery (“low tie”) or at the inferior mesenteric artery’s origin directly at the aorta (“high tie”). Obviously, the high-tie ligation enables removal of additional lymphatic tissue, but whether this confers an advantage in survival is still unclear. The study of Grinnell [59] demonstrated a non-significant survival advantage, although other studies showed no survival advantage after high-tie ligation of the inferior mesenteric artery [60–62]. Adachi and colleagues

investigated the distribution of lymph-node metastases along the inferior mesenteric artery [63]. Only in 1 of 135 patients (0.7%) was a positive lymph node found at the root of the inferior mesenteric artery [63]. Therefore, the authors concluded that high ligation of the inferior mesenteric artery for cancer of the sigmoid colon and rectum is not oncologically indicated [63]. However, Moerschel and colleagues clearly demonstrated the oncological consequence of central ligation of the inferior mesenteric artery at the aorta (significant increase of positive lymph nodes) with no increase of perioperative morbidity or mortality [64]. At present, there is no prospective controlled nor randomised study of high versus low ligation and there is no study accurately focussing on subsequent pelvic nerve injury. Nevertheless, in case of affected borderline lymph nodes, there is a high probability of infiltration of the paraaortic lymph nodes and, therefore, of disseminated disease. Even if oncological effectiveness of high-tie ligation of the mesenteric inferior artery is not generally accepted, it is often indispensable for technical reasons – to guarantee a tension-free anastmosis, particularly if a low anterior resection with straight coloanal or colonic pouch-anal anastomosis is performed.

Many studies focus on lateral clearance and total mesorectal excision. Following the studies of De Haas-Kock and colleagues [65] and Quirke and colleagues [66], local recurrence can result from microscopically incomplete radial resection. Following Heald and colleagues, who first published their results of total mesorectal excision with sharp dissection of the "Holy plane" [19], TME has been advanced as the "gold-standard" technique for anterior resection of the rectum considerably reducing local recurrence rates [67–71]. Therefore, the accepted policy of surgical treatment of carcinoma of the lower and middle third of the rectum is to perform TME as part of either anterior resection or abdominoperineal excision [71]. As reported by Rullier and colleagues [72], sphincter-saving resections can be performed for low-rectal cancer without an increased risk of local recurrence. Performing TME in sphincter-saving resections, a distal margin of 2 cm is proven to be oncologically sufficient. In general, the preferential treatment for carcinoma of the upper third of the rectum has also been TME, except where incurability or frailty militate against these principles [71]. Recently, Heald and colleagues reported a preference for treating lesions of the upper rectum with a less than full rectal excision, transecting the mesorectum 5 cm below the carcinoma [73]. The question whether TME should be routine for cancer of the upper rectum or the rectosigmoid is controversial due to a significant increase of morbidity [21, 51, 71]. The standard anterior resection for cancer of the rectosigmoid or upper rectum does, therefore, not include complete removal of mesorectum [51]. In the case of middle- or low-rectal cancer, intersphincteric resection with coloanal anastomosis can be performed if a distal tumour clearance of 2 cm can be achieved. The application of coloanal anastomosis has not compromised oncological results [74–76].

Following the results of Hida and colleagues, who recently examined the distal spread of rectal cancer within the mesorectum, lymph-node metastases could be detected up to 4 cm distal to the tumour in 20% of patients with T3 carcinoma [77]. With TME, all these positive nodes can be resected and sphincter preservation can be achieved in the majority of patients suffering from cancer of the middle rectum [78]. Moreover, the policy of TME, sphincter preservation and autonomic nerve-sparing surgery leads to a significant reduction in blood loss due to a dissection along tissue free of vessels. This aspect highlights the theoretical association between prognosis and blood transfusion [79].

It is a controversial issue whether an extended (lateral) lymphadenectomy should be performed in patients with tumours below the peritoneal reflection and at high risk for lymph-node metastases (T3 and higher) to achieve superior oncological results. The Japanese are the main proponents of this technique whereby the lateral and superior lymphatic systems are excised including high ligation of the mesenteric inferior artery and an extended lymph-node dissection of periaortic and pelvic nodes beginning at the duodenum and extending down to take the periaortic and lateral iliac lymph nodes [50, 80–82]. However, there are no prospective randomised studies of its effectiveness on local recurrence or survival. The main disadvantage of extended lymphadenectomy is the increase in morbidity, particularly as a result of pelvic nerve damage – sexual and urinary dysfunction. As a consequence of this disturbing morbidity, the Japanese have developed the technique "autonomic nerve-sparing" surgery, which aims to preserve the hypogastric and pelvic plexus without compromising tumour clearance [50, 80–82]. However, it is questionable whether the increased morbidity associated with extended lymph-node dissection justifies the results. Interestingly, oncological results of Sugihara and colleagues [80] do not differ from the results of McFarlane and colleagues [83] or Enker and colleagues [84] performing TME without lateral lymphadenectomy. Consequently, only one-third of patients with positive mesorectal lymph nodes would profit from extended lymphadenectomy and, therefore, extended lymphadenectomy cannot be recommended as a generally accepted standard procedure at the moment [51, 85].

New technologies

Local recurrence can result from microscopically incomplete lymph-node dissection. Therefore, detection of microscopically involved lymph nodes by radioimmunoguided surgery (RIGS) using tumour antigens, e.g. CEA and tumour-associated glycoprotein (TAG)-72, may be helpful for prediction of prognosis and for planning adjuvant ther-

apeutic modalities [86]. Recently, Nieroda and colleagues have reported their encouraging results of immune corrective surgery (ICS) as a procedure of selective lymphadenectomy based on the assumption that the immune competence of the organism is reduced by remaining tumour cells as well as by tumour antigen–antibody complexes [87]. The authors used a detection method that included an injection of radiolabelled antibody able to recognise the immune complex (tumour-associated antigen immune complexes are presented on follicular dendritic cells). In 20 patients (stages I–III disease) treated by means of ICS, there was a statistically significant survival advantage compared with patients treated using standard procedures [87]. The detection of micrometastases by ICS leads to an extended removal of remaining tumour tissue and improves the immune status of the patients. This field seems to be promising for the future, but is not practical in general at the moment.

The role of laparoscopic colorectal surgery for the cure of cancer

The current status of laparoscopic surgery for the cure of colorectal cancer is evolving and controversial [88, 89]. Initial short-term results of laparoscopic colectomy for cancer indicate that the minimally-invasive approach may not result in a higher incidence of cancer-related morbidity or recurrence rates than after conventional colectomy. However, being aware of the unsolved issue of port-site metastases, surgeons have to perform laparoscopic colorectal surgery for the cure of cancer only within prospective randomised trials. Long-term results must convincingly be shown to be oncologically equal to open curative procedures. However, at present, laparoscopic colectomy for cancer cannot be recommended as standard therapy for colorectal cancer.

Conclusions

Lymph-node dissection is a crucial part of radical surgery for colorectal cancer, essential for: staging and planning adjuvant therapy, potential curative therapy (R0) and prediction of prognosis. Standard lymph-node dissection is performed radicularly and follows the arterial supply. In the case of colon carcinoma located in between two drainage areas, extended lymphadenectomy is necessary. In rectal cancer, total mesorectal excision has enriched surgical therapy and should be performed as the standard procedure in middle and lower rectal carcinoma, whereas, extended lymphadenectomy cannot be generally recommended. Finally, the surgeon is an important prognostic factor in colorectal cancer surgery. New technologies in the detection of micrometastases are promising.

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