

Management of nodal disease from colon cancer in the laparoscopic era

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Accepted: 12 November 2014 / Published online: 22 November 2014
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Abstract

Purpose In colon cancer (CC), nodal involvement is the main prognostic factor following potentially curative (R0) resection. The purpose of this study was to examine data from the literature to provide an up-to-date analysis of the management of nodal disease with special reference to laparoscopic treatment.

Methods MEDLINE and EMBASE databases were searched for potentially eligible studies published in English up to July 15, 2014.

Results In CC, nodal involvement is a frequent event and represents the main risk of cancer recurrence. Node negative patients recur in 10–30 % of cases most likely due to underdiagnosed or undertreated nodal disease. Extended colonic resections (complete mesocolic excision with central vascular ligation; D3 lymphadenectomy) provides a survival benefit and better local control. Sentinel lymph node mapping in addition to standard surgical resection represents an option for improving staging of clinical node negative patients. Both extended resection and sentinel lymph node mapping are feasible in a laparoscopic setting.

Short summary Extended colonic resection and sentinel lymph node mapping play roles in the management of nodal disease from colon cancer, both of which can improve staging in node negative patients in a minimally invasive setting.

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Conclusions Both extended colonic resection and sentinel lymph node mapping should play a role in the laparoscopic treatment of CC with the purpose of improving control and staging of nodal disease.

Keywords Colon cancer · Lymph node metastasis · Complete mesocolic excision · Lymphadenectomy · Sentinel lymph node mapping · Laparoscopy

Introduction

Colorectal cancer (CRC), with 1.2 million cases and 600,000 deaths reported annually, is one of the most common cancers worldwide. According to recent estimates, CRC is the most common cancer and the second most common cause of cancer-related death in Europe [1].

Surgical resection is the mainstay therapy, with a laparoscopic approach rapidly becoming the treatment methodology of choice for colon cancer (CC) [2, 3]. Laparoscopic colonic resection has comparable oncological outcomes and better perioperative results compared with open surgery, especially in Enhanced Recovery After Surgery (ERAS) program settings [4–6].

After potentially curative surgery for CC, nodal involvement is the major determinant of prognosis and represents the main indicator for adjuvant chemotherapy [7–11]. Nonetheless, disease recurrence or progression develops in about 10–30 % of node-negative patients, most likely because of undetected or undertreated occult nodal disease [12–15].

Accordingly, several strategies have been proposed to improve staging and to control nodal disease. Some authors have proposed extended surgical resection (i.e., complete mesocolic excision [CME] with central vascular ligation [CVL]; D3 lymphadenectomy) [16–18], while others prefer adopting innovative strategies allowing for organ and function

sparing surgery (i.e., sentinel lymph node mapping [SLNM]) [19–21].

In this review, data from the literature on lymph node involvement were analyzed focusing both on the clinical impact and technical issues with the intention of proposing patient- and tumor-tailored lymphadenectomy with minimally invasive surgery.

Adopted criteria for lymph node staging

The AJCC/UICC staging system

In non-metastatic CC, lymph node involvement is the main prognostic factor. More specifically, the number of positive nodes has been accepted as the most valuable, reproducible, and easy to use predictor of disease recurrence and prognosis [22, 23].

The actual American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) staging system considers pN category according to the absolute number of involved regional nodes. Regional nodes are determined according to the location of the tumor and includes nodes located adjacent to the colon, along the vascular arcades of the marginal artery, and along the course of the major vessels supplying the colon. Specifically, the regional lymph nodes are the pericolic and those found along the ileocolic, right colic, middle colic, left colic, inferior mesenteric, and superior rectal arteries [24].

Though the seventh Edition of the AJCC/UICC staging system includes substantial changes from previous editions, which are particularly complex for stage II and III disease, controversy still exists with respect to its ability to address all survival discrepancies observed in CC [25–27].

The JSCCR staging system

The Japanese Society for Cancer of the Colon and Rectum (JSCCR) staging system considers the pN categories according to the number and site of nodal involvement. Regional lymph nodes consist of three groups: pericolic, intermediate, and main lymph nodes. The extent of regional lymph nodes varies according to the anatomical location of the primary tumor in relation to its feeding arteries. Pericolic nodes are lymph nodes along the marginal artery; intermediate nodes are lymph nodes along colic arteries (ileocolic, right colic, right middle colic, left middle colic, left colic, and sigmoid arteries). Main nodes are lymph nodes at the origin of each colic artery for those tumors located in the superior mesenteric artery territory or proximal to the origin of the left colic artery for those tumors located in the inferior mesenteric artery territory. When present, lymph node metastases are classified as follows: N1, metastasis into one to three pericolic or intermediate

lymph nodes; N2, metastasis in four or more pericolic or intermediate lymph nodes; and N3, metastasis in main lymph nodes.

Accordingly, the extent of lymphadenectomy is defined as D1 when lymph node dissection is limited to pericolic nodes; D2 when lymph node dissection entails complete dissection of pericolic and intermediate nodes, and D3 when lymph node dissection is extended to all regional nodes. Hence, D3 lymphadenectomy entails the removal of lymph nodes along the superior mesenteric artery in right-sided CC and removal of lymph nodes proximal to the inferior mesenteric artery in left-sided CC (Fig. 1) [28].

Importance of number of analyzed nodes

The evaluation of at least 12 nodes is recommended by the AJCC/UICC staging system, and this suggestion is accepted by the great majority of authors. Nonetheless, population-based as well as many multicenter studies report that less than 50 % of patients with CC receive adequate lymph node evaluation [13–15, 29–31]. In this setting, adjuvant chemotherapy is proposed to pN0 patients with less than 12 analyzed nodes because of high recurrence rates demonstrated in previous studies [32–34].

Besides stage migration (Will Rogers phenomenon), a positive association between the number of analyzed nodes and long-term outcome in stage II and III CC has been reported in several reports [35–37].

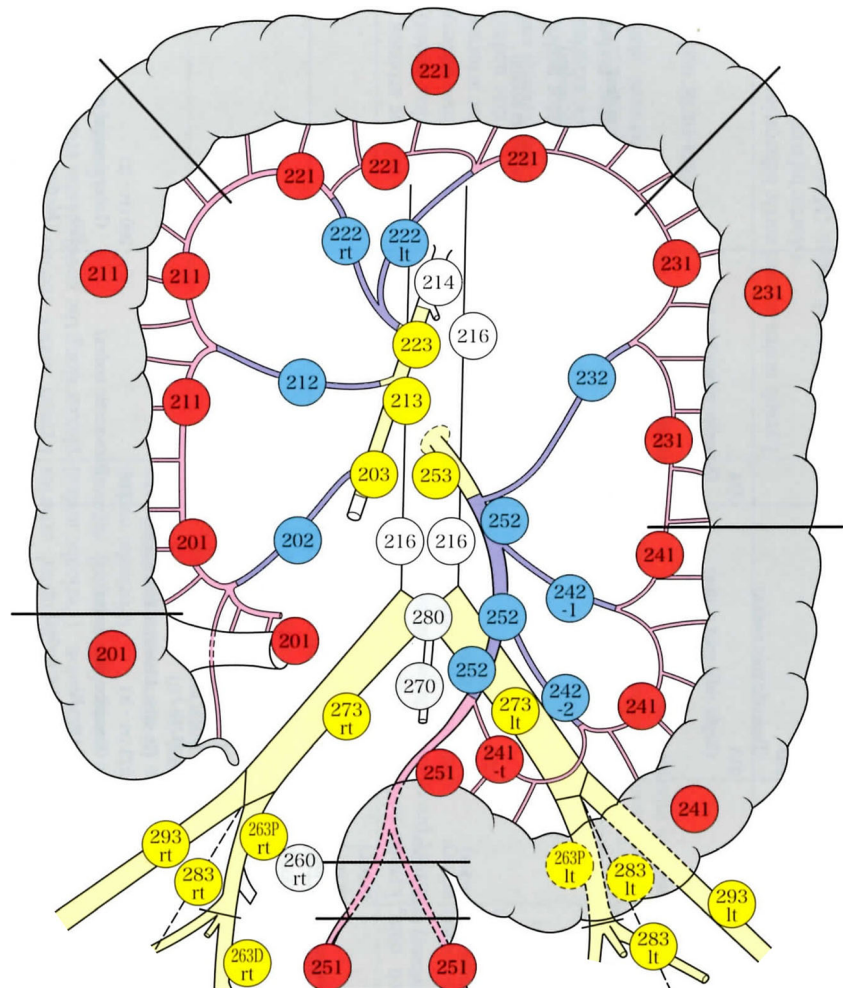
Gleisner et al., using Surveillance, Epidemiology, and End Results (SEER) data from 1998 to 2007 with 154,208 patients, demonstrated that the total number of nodes examined was associated with long-term outcome. More specifically, total nodal count was associated with a non-linear decrease in the risk of death. Among node-negative patients, the risk of death decreased considerably for each negative node up to 20–25 lymph nodes examined. Among node-positive patients, the risk of death increased with the number of positive nodes independent of the number of nodes analyzed. However, when the number of analyzed nodes was less than 10–15, the risk of death was higher than predicted by the independent effect of total nodal count or number of positive nodes [38].

Budde et al. recently confirmed the association between higher lymph node counts and better survival using data from the 2004 to 2010 SEER database on 147,076 patients [39].

Pathologic assessment of nodal disease

Lymph node search via manual dissection of fatty tissue and hematoxylin and eosin (HE)-stained histological examination of the largest cut surface remain the standard approach in pathological lymph node evaluation. However, some nodes remain undetected and only a small portion of analyzed nodes is assessed, leaving most parts of the identified nodes

Fig. 1 Lymph node classification according to the Japanese Society for Cancer of the Colon and Rectum (JSCCR). Level 1 lymph node stations are represented in red, level 2 lymph node stations in blue, and level 3 lymph node stations in yellow. (Modified from: *Japanese Society for Cancer of the Colon and Rectum (JSCCR). Japanese Classification of Colorectal Carcinoma, 2nd English Edition, Kanehara & Co., Ltd., Tokyo 2010*) [28]



unexamined. This undoubtedly leads to understaging of the disease, and it partially explains the 10–30 % recurrence rate observed in stage I and II CCs [40].

Adopting additional sections and immunohistochemistry (IHC) may improve the identification of positive lymph nodes. Of note, many patients who are initially staged as lymph node-negative and experience disease recurrence have isolated tumor cells (ITCs) or micrometastases (MMs) after advanced evaluation [41, 42]. Similarly, molecular analysis of lymph node tissue has been introduced as an additional tool in the work-up of cancer patients. This technique allows identification of minimal disease in lymph nodes by examining the entire node, thereby overcoming the problem of sampling bias. Importantly, the molecular detection of tumor cells in regional lymph nodes has been associated with disease recurrence and poor survival in node-negative patients [43]. Nonetheless, some drawbacks exist in adopting these techniques in actual clinical practice. For instance, analysis of multiple HE- and IHC-stained sections is expensive and time-consuming, and it is difficult to adopt for every retrieved lymph node. Moreover, molecular analysis has not yet been standardized; it is expensive, and some false-positive results have been

described [44]. Furthermore, although positive lymph nodes are usually those nearest to the primary tumor, analysis of unselected nodes can lead to false-negative results [45].

Micrometastases and isolated tumor cells

The AJCC/UICC staging system recommends evaluating the presence of MMs or ITCs in CC specimens, although these categories have not yet been included in the actual TNM classification. ITCs are defined as the presence of a single or small number of tumor cells equal of less than 0.2 mm in diameter, while MMs are described as the presence of deposits equal to or less than 2.0 mm, but greater than 0.2 mm in diameter. MMs and ITCs, whether detected by standard histologic techniques or IHC, are coded as pN0 (i+), and a tumor that is detected only by special molecular techniques such as reverse transcriptase polymerase chain reaction (RT-PCR) is coded as pN0 (mol+) [24]. The AJCC/UICC recommendations do not explicitly indicate the method to use to detect occult disease. For this reason, some authors have strictly adopted HE and IHC while molecular analysis is employed by others [43, 44, 46].

The presence of occult malignant cells, either in the form of ITCs or MMs, has been demonstrated in 25–58 % of node-negative CRC patients depending on their characteristics and method of detection used [42, 43, 46–48]. Although the prognostic value of these methods or techniques has not yet been completely clarified, occult disease remains of great interest, since it may represent a possible indication for adjuvant chemotherapy in the near future.

Nodal tumor deposits

The actual AJCC/UICC staging system uses the term “satellite tumor deposits” to designate discrete rounded nodules of tumor cells of any size within the pericolic fat or in adjacent mesentery. They are considered the equivalent of nodal metastases, even if they lack residual nodal architecture, and staged as N1c disease in the absence of other nodal metastases. Each should be counted separately for the involved lymph node count that determines pN status.

The presence of tumor deposits is a strong adverse prognostic feature [25, 49]. The prognostic impact was addressed in a recent study by Ueno et al. in which they analyzed the optimal categorization of nodal tumor deposits and reported presence in 17 % of 3,958 colorectal cancer patients. The recommendation of the AJCC/UICC for considering nodal tumor deposits as nodal metastases irrespective of contours was therefore confirmed [50].

Lymph node involvement

Roughly 60 % of CCs show nodal involvement upon histopathological examination [51]. However, the great majority of studies do not show an increase in nodal positive count in relation to the number of analyzed nodes, unless a very small number of nodes are analyzed [36]. Nonetheless, nodal count is clearly associated with survival advantages [37–39]. Furthermore, when considering the relationship between lymph node count and positivity, many confounding factors may affect the results [36, 52].

In Western countries, since it is not strictly required in a clinical setting, the location of nodal metastases is usually not recorded, and this may represent a major limitation for deep knowledge of the disease. Understanding lymphatic drainage of the colon is challenging because of its variety and complexity; however, it is generally accepted that the lymphatic tracts tend to accompany supplying arteries of the colon. Because of the diversity of blood supply, particularly in the right and transverse colon, it is difficult to detect clear margins of lymphatic drainage for each colon segment. A clear and precise classification of lymph node areas according to the

location of the tumor may therefore generate very useful information.

Figure 2 shows data on the level of lymph node involvement according to the JSCCR classification for right, transverse, left, and sigmoid colon.

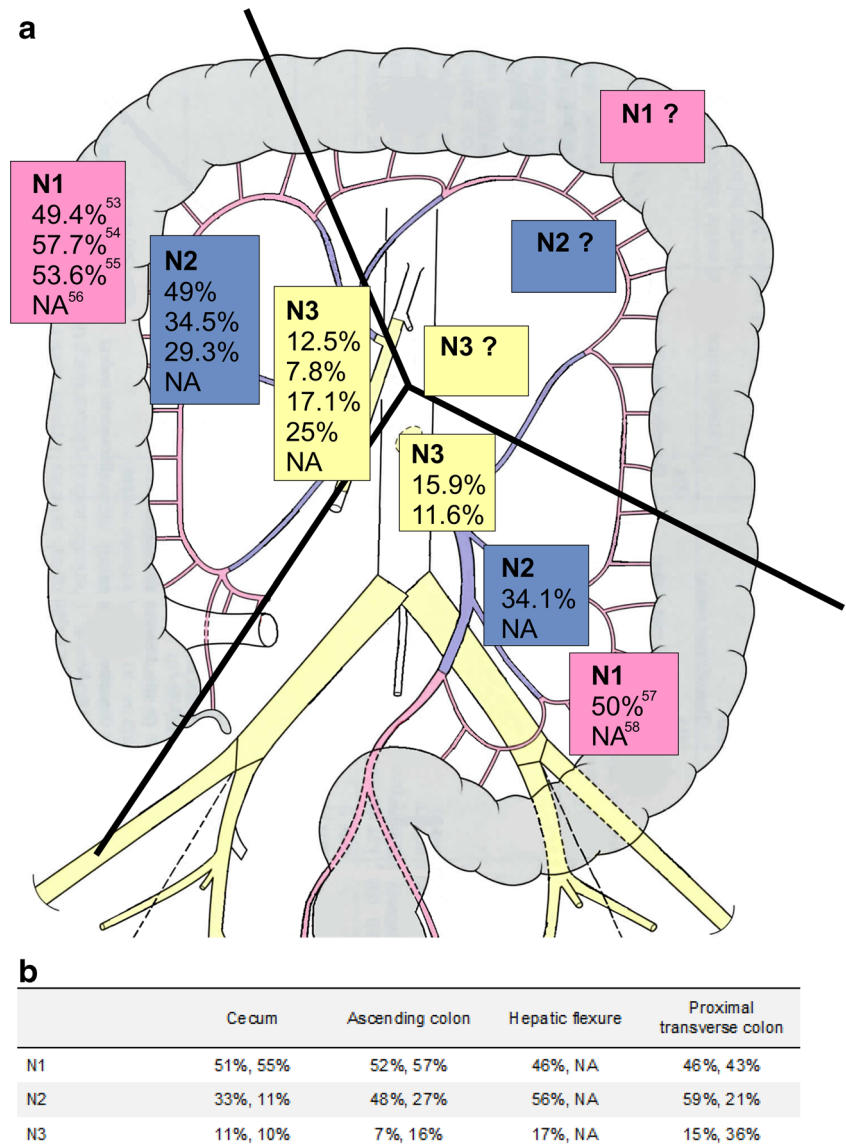
Complete mesocolic excision with central vascular ligation

After total mesorectal excision (TME) was introduced, local recurrence rate as well as prognosis improved significantly in rectal cancer [59, 60]. In fact, the observation that a better prognosis for rectal cancer compared with CC was observed in some countries after adopting TME leads Hohenberger et al. to hypothesize that CC surgery may be improved by implementing the concept of surgical dissection along embryological planes. With this concept, the integrity of the embryological envelope around the mesocolon is maintained, allowing maximal lymph node retrieval and minimizing the possibility of cancer cell seeding. This represents the idea of CME. The accompanying concept of CME in Hohenberger et al.’s idea was CVL, obtained through the division of supplying arteries at their real origin after completing colonic mobilization and dissection along the main vessels [16].

For cecum and ascending CC, division of ileocolic and right vessels is obtained at the origin with the superior mesenteric artery and vein, while division of middle colic vessels is obtained at the origin of the right branches. For transverse CC, including right and left flexures, division of the middle colic vessels is obtained through central ligation of the middle colic artery and vein considering possible anatomical variations. Additionally, central division of the right gastroepiploic artery and vein may be accomplished using this approach. For cancer of the right flexure, division of the colon is performed in proximity to the left flexure. For cancer of the transverse colon and left flexure, the descending colon is also sacrificed. For cancer of the proximal descending colon, the root of the superior mesenteric artery is usually preserved, and division of the left colic artery is obtained at its origin. For cancer of the middle descending colon down to the sigmoid colon, the root of the inferior mesenteric artery and the inferior mesenteric vein below the pancreas are divided. The proximal colonic division is performed between the distal transverse colon and the distal descending colon depending on the site of the tumor [16].

West et al. demonstrated that CME with CVL specimens are characterized by more tissue compared with standard surgery in terms of distance between the tumor and vascular tie, length of bowel removed (both colon and terminal ileum), and area of mesentery. Importantly, CME with CVL allows more mesocolic plane resections (92 vs. 40 %) and a greater number of nodes analyzed (30 vs. 18). According to West et al.’s hypothesis, these differences may explain the 15 %

Fig. 2 a Level of lymph node involvement for node positive patients according to the JSCCR classification for right colon, transverse colon, left colon, and sigmoid colon [53–58]. **b** Level of lymph node involvement for node positive patients according to the JSCCR classification for right colon segments [53, 55]



survival advantage observed at 5 years as reported in a previous study on the completeness of mesocolon resection [61, 62].

Recently, West et al. demonstrated that Japanese D3 resection and CME with CVL are comparable in terms of quality of mesocolic plane resection and distance between main ties and tumor area. In Japanese experience, according to JSCCR guidelines, the extent of longitudinal resection was significantly shorter; hence, total nodal count and mesentery area were less represented [63]. Differences in the extent of colonic and lymph node resection between D3 lymphadenectomy according to JSCCR guidelines and CME with CVL according to Hohenberger et al.’s idea are exemplified in Fig. 3. JSCCR guidelines suggests D3 lymphadenectomy for clinical T3 and T4 tumors or clinical evidence of lymph node

metastasis [16], while Hohenberger et al. offer CME with CVL even in early tumors [17].

Several experiences from Eastern countries have demonstrated the feasibility and safety of laparoscopic extended colonic resections (either CME or D3 lymphadenectomy) for CC. Table 1 reports short- and long-term results of the main studies. While in countries from the Far East, such as Japan or Korea, the concept of preservation of the mesocolic plane and lymph node clearing are strictly respected, many surgeons in the United States and Europe argue there are not enough data for this procedure to be performed [68].

In the original study by Hohenberger et al. on 1,438 patients submitted to CME with CVL for CC, the mean number of retrieved nodes was 32. A prognostic cut-off value for the number of analyzed nodes was computed according to the “Le

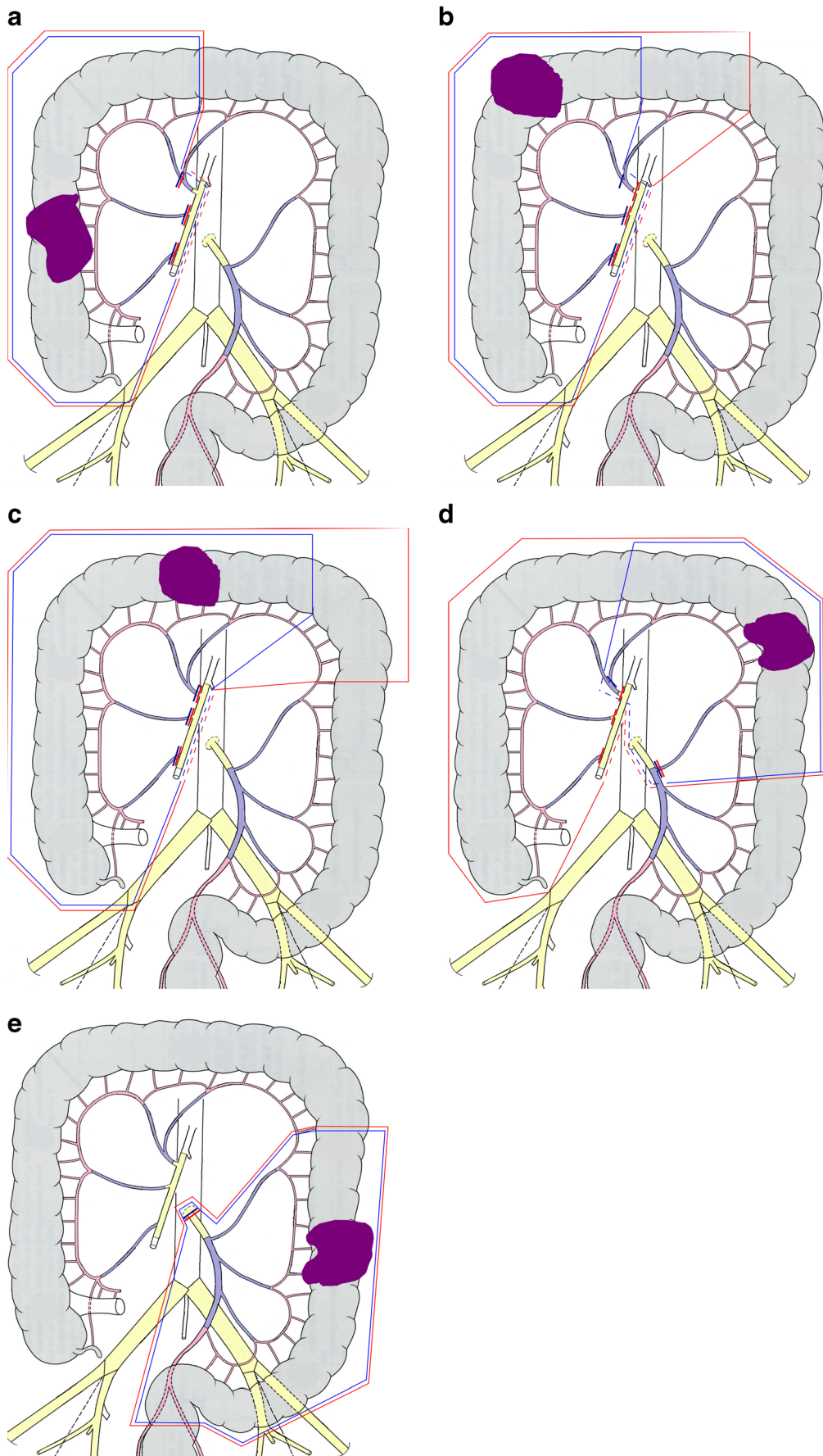


Fig. 3 Extent of colonic and lymph node resection according to JSCCR guidelines (*blue line*) [16] and CME with CVL according to Hohenberger idea (*red line*) [28]

Blanc” method, and a value of 28 was demonstrated both in node-negative (682) and node-positive (383) patients. The survival benefit when more than 28 nodes were analyzed was 5.6 % for node-negative patients (96.3 vs. 90.7 %) and 7.1 % for node-positive patients (71.7 vs. 64.6 %) [16].

In accordance with these results, Kotake et al. recently demonstrated an 18 % advantage in 5-year survival rate in patients with pT3 and pT4 CC after D3 compared with D2 lymphadenectomy. The mean number of nodes analyzed was 15 and 23 after D2 and D3 lymphadenectomy, respectively [69].

Sentinel lymph node mapping

The first lymph node or group of nodes along the route of lymphatic drainage of a primary tumor is known as the sentinel lymph node (SLN). Since the concept of SLN mapping (SLNM) was demonstrated in a clinical study involving patients with malignant melanoma, the clinical impact of SLNM has become a major topic with regard to various solid tumors.

While SLNM is widely adopted in melanoma and breast cancer and prevents unnecessary lymphadenectomies, its application for gastrointestinal malignancies meets resistance because of the multidirectional lymphatic flow and the possibility of skip metastases that characterize the gastrointestinal tract [57, 70].

However, although some authors recommend adopting SLNM to minimize the extent of resection in early-stage CC [71, 72], it is actually proposed with the aim of improving

nodal staging in the setting of a standard lymph node dissection by carefully evaluating a restricted number of lymph nodes. Therefore, SLNM has to be considered as a technique for potentially improving CC staging without defined prognostic impact and therapeutic implication [73, 74].

Unfortunately, SLNM has not yet been standardized, and many differences exist regarding indications, methods, and materials, making inter-study comparisons very difficult and delaying its application in normal clinical practice. Additionally, the results seem to be very much influenced by the experience of the operating surgeon with a learning curve that has been described to be as high as 20–30 cases [75–77].

Techniques for sentinel lymph node mapping

In vivo SLNM consists of the detection of SLNs before colonic resection by using peritumoral injection of dye agents or radiotracers (i.e., ^{99m}Tc). SLNs are identified by directly visualizing colored nodes or intraoperative lymphoscintigraphy.

Blue-dye SLNM is the most used method; blue-dye agents are injected subserosally at the time of surgery or submucosally via intraoperative or preoperative colonoscopy, with injected volumes varying from 0.5 to 5.0 mL. Several blue-dye agents have been used, without any differences between them (i.e., methylene blue, patent blue, sulfan, and isosulfan blue). Regarding dye agents, some limitations have been described, such as injections should be performed prior to colonic mobilization, observation of coloration has to be done in real-time, and visualization of stained nodes is difficult in obese patients, right-sided CC, and small tumors, particularly during laparoscopic surgery [72, 78].

Radiotracer-guided SLNM has been applied to improve the accuracy of SLN detection. Radiotracer ^{99m}Tc -injection is

Table 1 Main characteristics and results of studies reporting on laparoscopic extended colonic resection (i.e., CME with CVL; D3 lymphadenectomy)

Author (country)	Accrual period (no. of pts)	Tumor location	cTNM stage	Type of resection	No. of yielded nds ^c	% of N+ (% of N3+) ^f	Morbidity (mortality) ^f	Overall rec (local rec) ^f	5-year survival ^f
Liang et al. (Taiwan) [57]	2000–2006 (98)	LC ^a	III	D3	27.4	89.8 (14.3)	22.4 (0)	28.6 (0)	NA
Gouvas et al. (Greece) [64]	2006–2010 (49)	CC ^b	I–III	CME	33/39/27 ^d	28.6 (NA)	NA	NA	NA
West, Kobayashi et al. (Japan) [63]	2009–2011 (31)	CC	I–III	D3	24/19 ^e	NA	NA	NA	NA
Adamina et al. (United States) [65]	2005–2010 (52)	RC	I–III	CME	22	26.9 (NA)	30.8 (0)	8.3 (0)	NA
Feng et al. (China) [56]	2010–2011 (35)	RC	II–III	CME	19	57 (NA)	8.6 (0)	NA	NA
Han et al. (China) [66]	2003–2010 (177)	RC	I–III	D3	15.2	32.8 (NA)	13 (0)	15.2 (2.8)	70.4
Shin et al. (S. Korea) [67]	2006–2009 (168)	CC	II–III	CME+D3	27.8	48.2 (NA)	17.8 (0)	11.9 (3.6)	89.6

^a Tumors of the distal sigmoid colon, rectosigmoid junction, and upper rectum were included

^b Tumors of the middle transverse colon and left flexure were excluded

^c Numbers with decimals are means whilst whole numbers represent medians

^d Numbers refer to tumors of the right colon/right flexure and proximal transverse colon/left colon

^e Numbers refer to tumors of the right, right flexure, and proximal transverse colon/left colon

^f Numbers are percentages

usually performed submucosally using preoperative colonoscopy, and intraoperative localization of hot nodes is then performed using a gamma probe. The radio-colloid method has shown comparable results in terms of detection rate and sensitivity with several practical limitations, such as the requirement of radiation safety regulations and specific equipment not always being available in community hospitals together with the need for an adjunctive colonoscopy. Furthermore, current available rigid-type laparoscopic gamma probes are fixed by the trocar, thus the freedom to search for sentinel nodes and to avoid the “shine through” effect from the injection site is seriously restricted [79–81].

Ex vivo SLNM was first described by Wong et al. [82] and consisted of the detection of SLNs by blue-dye injection in fresh specimens early after resection. Wong et al. described the use of 0.25 mL isosulfan blue injected submucosally using a tuberculin syringe into four quadrants around the tumor after incision of the antimesenteric border of the colon [82]. Moreover, subserosal injection of other dye agents (i.e., methylene blue, patent blue, and sulfan blue) have been used with comparable results [73, 74].

No differences in detection rates or sensitivity have been described between in vivo and ex vivo techniques (Table 2), though some authors report a higher detection rate after adding ex vivo techniques in SLN-negative cases [72, 74].

In vivo techniques have the potential advantage of evaluating aberrant lymphatic drainage, which has been described to occur in 4–29 % of patients [20, 74, 90, 91]. Recently, Saha et al. performed a prospective study focused on detecting aberrant lymphatic drainage and its impact on the extent of surgery. Of 192 patients, 44 (22 %) underwent extended resection caused by aberrant lymphatic drainage, and in 19 of these cases (10 %), one or more positive SLNs were found outside the standard resection field. Moreover, SLNs were the only site of nodal metastasis in two patients [20].

The ex vivo technique has the advantage of being completely safe for the patient eliminating the low but present risk of allergic reactions that have been described in 0.5–2.5 % with patent blue and 0.9–1.9 % with isosulfan blue. No allergic reactions have thus far been described with methylene blue [92–94].

Indocyanine green (ICG) is a near-infrared (NIR) fluorophore that has shown promising results in SLNM in gastrointestinal as well as non-gastrointestinal neoplasias (i.e., lung, bladder, uterus, breast, etc.). ICG may represent an ideal tracer because of the lack of endogenous NIR tissue fluorescence and because it does not alter the normal surgical field as it is invisible to the human eye. However, special imaging systems are required to visualize NIR fluorescent light [95]. However, several NIR imaging systems for open and laparoscopic surgery are presently available. Nagata et al. first described ICG application in laparoscopic SLNM of

colorectal cancer in 2006 [87]. The main advantages of ICG compared with the blue-dye and radiotracer methods relate to the real time and better visualization of lymphatic vessels and SLNs embedded deep inside tissues without the risk of radioactivity. The advantage of deep penetration in fatty tissue of NIR fluorescent light is particularly beneficial in obese patients [96].

Histopathological examination of sentinel lymph nodes (HE, IHC, PCR)

Upstaging in CC is the most inviting idea in the SLNM concept. About 10–30 % of node-negative patients develop disease progression or recurrence, most likely due to the presence of occult tumor cells [7–10]. In-depth analysis through serial sectioning, IHC, and RT-PCR has demonstrated 5.7–46.5 % upstaging of pN0 CCs with SLNM may facilitate pathologic examination, making this technique more applicable, since in-depth analysis is focused on one to a few nodes [21, 75, 83, 86, 89]. Many studies have confirmed the validity of SLNM in this setting with meta-analyses showing a mean upstaging of 15 and 19 % [73, 74].

Braat et al. recently reported very high survival rates for node-negative CC patients with negative SLNs with a 5-year disease-free survival rate approaching 95 %. These results seem to confirm the use of SLNM in discriminating patients with very good prognoses [97].

Sentinel lymph node mapping in open surgery

Two systematic reviews and meta-analyses by van der Pas et al. in 2011 [73] and van der Zaag et al. in 2012 [74] evaluated SLNM in colorectal cancer. The two papers included almost exclusive studies from open surgery using blue-dye and radiotracer or the combination of both methods; substantial result homogeneity was demonstrated among different techniques. The pooled detection rate for colorectal cancer was 94 and 91 %, while overall sensitivity was 76 and 86 %, respectively [73, 74]. van der Zaag et al. showed significantly higher sensitivities for T1 and T2 compared with T3 and T4 colorectal cancers (93 vs. 59 %) [74]. Conversely, stratification by stage limited to CC showed no significant difference in sensitivity among T1, T2, T3, and T4 tumors in the meta-analysis by van der Pas et al. [73]. Interestingly, van der Pas et al. selected eight studies with high-quality SLN procedures that had a detection rate and sensitivity for CC of 96 and 90 %, respectively [73].

Both studies concluded that SLNM should be considered as an additional procedure to be performed in addition to standard resection with the purpose of improving staging of clinical node negative patients [73, 74].

Table 2 Main characteristics and results of principal studies reporting on laparoscopic and open sentinel lymph node mapping in colon cancer (SLNM)

Author (country)	Accrual period (no. of pts)	cT	No. of lap.	In vivo/ex vivo surgery	Tracer ^b	Histology	Detection rate ^a	Sensitivity ^a	Upstaging ^a	ALD ^a
Saha et al. (US) [83]	1996–2004 (408)	T1–T4	0	In vivo	IB	HE, IHC	99.3	89.4	26.1	NA
Bembenek et al. (Germany) [75]	2003–2005 (315)	T1–T4	22	In vivo	PB	HE, IHC	85.1	53.7	21.3	1.6
Lim et al. (US) [84]	1998–2006 (199)	T1–T4	0	In vivo	IB+ ^{99m} Tc	HE, IHC	99.2	58.3	NA	0
Faerden et al. (Norway) [85]	2000–2005 (199)	T1–T4	0	In vivo	PB	HE, IHC	92.5	53.3	NA	NA
van der Zaag et al. (NDL) [86]	2006–2008 (100)	T1–T3	36	Ex vivo	PB	HE, IHC	92	83	29	0
Nagata et al. (Japan) [87]	2002–2004 (48)	T1–T3	48	In vivo	ICG	HE	97.9	53.8	NA	NA
Bianchi et al. (Italy) [72]	2006–2011 (75)	NA	75	In vivo/ Ex vivo	PB	HE	93.4	77.7	NA	5.3
Hirche et al. (Germany) [88]	NA (26)	T1–T3	11	Ex vivo	ICG	HE, IHC	96.2	81.8	33.3	0
Sardón Ramos et al. (Spain) [89]	2009–2011 (125)	Tis–T4	71	In vivo	MB	HE, IHC	97.6	83.3	5.7	0

^aNumbers are percentages

^bTumors of the distal sigmoid colon, rectosigmoid junction, and upper rectum were included

IB isosulfan blue, PB patent blue, MB methylene blue, ^{99m}Tc technetium-99m, ICG indocyanine green, ALD aberrant lymphatic drainage

Laparoscopic sentinel lymph node mapping

There is great interest in laparoscopic SLNM as it is becoming the preferred approach for CC treatment. In 2002, Tsioulis et al. first reported the adoption of SLNM in laparoscopically assisted colectomy for CC. In 2003, Bilchik et al. reported using the same protocol with increased numbers (30 cases) of laparoscopic SLNM using isosulfan blue injected submucosally through intraoperative colonoscopy (27 cases) or subserosally using a spinal needle (three cases); their detection rate was 100 %, sensitivity 75 %, and upstaging 14 %, and aberrant lymphatic drainage was described in 29 % of the cases [91].

In two distinct Italian experiences, Bianchi et al. reported laparoscopic SLNM using patent blue or radiotracer [72, 98]. In the more recent study, 75 patients affected by stage I and II CC were enrolled. Blue-dye was the used method with injection performed subserosally at the time of surgery. The detection rate was 93 %, while the false-negative rate was in 22 %. Eight more patients underwent SLNM guided by radiotracer ^{99m}Tc that was injected submucosally through colonoscopy the day before surgery. With this approach, the detection rate was reported to be 100 %, and no false-negatives were reported [72].

In 2006, Nagata et al. reported on the use of ICG and NIR laparoscopic light for SLNM of CC and cancer of the upper rectum. A detection rate of 98 % was reported together with

the absence of false negative cases in T1 and T2 patients. The false-negative rate for T3 tumors was 32 % [87].

Hirche et al. published the results on 26 CC patients who underwent open (15 cases) and laparoscopic assisted (11 cases) colonic resection with in vivo SLNM using NIR navigation and ICG. The detection rate, sensitivity, and upstaging were 96, 82, and 33 %, respectively [88]. In laparoscopic-assisted resections, ICG injection was accomplished intraoperatively after mini-laparotomy.

Most recently, van der Pas et al. reported 14 patients with CC treated by laparoscopy with intraoperative subserosal injection of ICG/albumin solution obtained using a spinal needle or an endoscopic flexible needle (Wang needle). The lymphatic flow and SLNs were identified using a NIR laparoscopic system, and the detection rate was reported to be 100 %. All the SLNs were negative by histopathological examination, but four cases had metastasis in non-sentinel nodes. It is possible that these results were due to the high percentage of T3 tumors (71 %) included in this cohort [96].

Conclusions

In CC, lymph node involvement is a frequent event, and it represents the main predictor of long-term survival and recurrence. As many as one in every four node-negative patients

experience recurrence after potentially curative resection because of underdiagnosed and/or undertreated nodal disease. Extended colonic resections (i.e., CME with CVL and D3 lymphadenectomy) seem to offer a survival benefit and better local control. SLNM, in addition to standard surgical resection, may represent an option for improving staging in clinical node-negative patients. Both extended resections and SLNM are feasible in a laparoscopic setting.

Acknowledgments The authors thank Tiziano Leso for editing figures and tables.

Conflict of interests None declared

Research funding None declared

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