Review Article

The impact of D2 lymphadenectomy on pathology understaging of right colon cancer

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Abstract: The question of how extensive lymphadenectomy should be in right colon cancer (RCC) surgery remains widely debated in the literature. A correct evaluation of the lymph node status of the surgical specimen is essential for staging and need for adjuvant therapy. Surgery and lymph node assessment are both important factors that influence the lymph node staging. Currently the European and American guidelines recommend the removal of a minimum number of 12 lymph nodes while the Japanese guidelines suggest modulating lymphadenectomy according to the stage of the disease. D2 lymphadenectomy can lead to downstaging of the disease due to several physiopathological mechanisms. The aim of this manuscript is to show the different factors that play a role in a better pathological evaluation of the lymph node status for RCC.

Keywords: Colon cancer; right hemicolectomy; lymphadenectomy; complete mesorectal excision (CME); surgery

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Introduction

The question of how extensive lymphadenectomy should be in right colon cancer (RCC) surgery remains widely debated in the literature.

Following the already known principle that the number of lymph nodes removed is a positive prognostic variable (1), Hohenberger *et al.* first proposed an extension of lymphadenectomy along with the correct embryological anatomical planes therefore practicing a complete mesorectal excision (CME) with a central vascular ligation (CVL). The aim was to improve the lymph node yield (median number of 32 lymph node per patient) and the oncological outcome: locoregional recurrence was reduced from 6.5% to 3.6% with a 5-year cancer-related survival rate of 85% (2).

Following standardization of the CME technique, several authors have started to practice a more extensive lymphadenectomy for the RCC than was practiced in the pre-CME era.

The nomenclature "D" for colon lymphadenectomy is relatively recent and used in the Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines to differentiate the extent of lymph node harvesting in relation to tumor infiltration and nodal positivity (3).

The absence of the description of a standardized technique for D2 lymphadenectomy (removal of pericolic nodes and intermediate nodes) in the literature, the description of different techniques performed to achieve the D3 lymphadenectomy (removal of nodes at the root of the regional artery plus D2 nodes dissection) and the latter's differences in practice between West and East (4) have generated a state of misunderstanding about of how extensive the lymphadenectomy of the right colon must be

and the correct procedure to perform.

It is well established that a correct evaluation of the lymph node status of the surgical specimen is essential for staging and need for adjuvant therapy.

Surgery is just one of the factors that influence the evaluation of lymph node status.

The aim of this manuscript is to show the different factors that play a role in a better pathological evaluation of the lymph node status for RCC.

D-lymphadenectomy for RCC surgery: a debate of East and West

Hohenberger *et al.* in 2009 was the first to propose some oncological principles for colon resection as it had been done several years earlier by Heald for resection of the rectum (2,5).

However, his technique had a complication rate of 19.7% (9.5% of emergencies) and a postoperative mortality rate of 3.1%.

JSCCR guidelines suggested to differentiate the extent of lymphadenectomy based on tumor wall invasion and lymph node metastases diagnosed by preoperative or intraoperative findings (6).

Even today the same guidelines suggest the following lymphadenectomy in relation to TNM stage for colon cancer:

- D0 and D1: cTis;
- D2: cT1, cT2;
- D3: cT2, cT3, cT4 and/or cN+ (3).

The European Society of Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) guidelines recommend the removal of regional lymph nodes around the arterial arcades in a minimum number of 12 for adequate pathological staging (7-9).

The minimum number of 12 lymph nodes was proposed in 1990 by the Working Party Report to the World Congress of Gastroenterology (10). This number was only partially supported by evidence, in fact several authors later proposed different minimum numbers of lymph nodes to be harvested in RCC (11).

Therefore, the differences between East and West in the approach to lymphadenectomy in the RCC are both terminological and conceptual.

In Japan, D3 lymph node dissection has become the standard for stage II and III colon cancer since the 1980s.

West *et al.* showed that the high quality of mesocolic surface and the distance between the high vascular tie and the colon wall were similar in both European and Japanese specimens, although the Japanese ones had a lower quantity of mesentery and lymph nodes (12).

Furthermore, while for the West the CVL with a lymphadenectomy extended to the root of the vessels has mostly a staging and prognostic sense, given the poor advantage on survival, for the East it would seem to have a therapeutic sense too, avoiding to leave lymph node metastases in place (4).

Therefore, the extension of the lymphadenectomy for the right colon and its indications would seem to be more standardized in the East than in the West.

These discrepancies between East and West on terminology, indications and surgical technique have caused little clarity about how extensive lymphadenectomy should be for RCC.

The specimens coming from CME and CVL procedure had an average difference of 41 mm in terms of distance between tumor and high vascular ligation and an average mesocolic surface more extended by about 52% compared to those operated with the classical technique (13).

Perhaps therefore the classical western hemicolectomy, the D3 lymphadenectomy practiced in the East and the CME with CVL practiced by Hohenberger *et al.* are three different procedures in terms of anatomical specimens.

The different lymph node groups to be removed in each type of lymphadenectomy for RCC could be defined according to the description of the nodal groups reported in the General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus (*Table 1*) (14).

Pathological mechanisms influencing lymph node staging: the problem of the risk of lymph node downstaging

Metastatic lymph node disease can be classified into isolated tumor cells (ITCs, <0.2 mm), micrometastases (from 0.2 to 2 mm) and macrometastases (>2 mm) (15).

Nodal staging also depends on the TNM staging system used. Micrometastases and macrometastases are considered as N+ in the TNM5–7 classifications (1998 to present); the ITCs are considered N+ by the TNM5, and N0 (i+) in the TNM6–7 staging system, thus modifying the subsequent therapy (16,17).

The three pathological mechanisms that can influence lymph node staging are micrometastasis, “stage migration” and “skip metastases”.

In colon cancer surgery from one to five lymph nodes

Table 1 Lymph node groups removed in each type of lymphadenectomy for RCC

Lymphadenectomy	Lymph node stations removed
D1	Epicolic and paracolic nodes within 5 cm from the tumor
D2	Epicolic and paracolic nodes between 5 and 10 cm from the tumor, intermediate nodes, ileocolic nodes, right colic nodes, middle colic nodes
D3	All lymph nodes removed for D1 and D2 plus lymph nodes at the roots of ileocolic, right colic and middle colic arteries
D4	All lymph nodes removed for D1, D2, D3 plus should be considered removal of central nodes

RCC, right colon cancer.

of the surgical specimen could present micrometastases so small that they would not be reported as positive, leading to an important understage ("stage migration") of the disease (stage I–II instead of III) (18,19).

Moreover, it is shown that in 19% of the patients the lymph node metastases do not always follow a linear pattern, but sometimes a jump one ("skip metastases"); it is possible to find lymph node metastases at station 3 without there being any in stations 1 and/or 2 (20,21).

About 4.5% of patients would be downstaged by a conventional lymphadenectomy (D2), compared to a D3 one (20).

Furthermore, it has been shown that the lymph node ratio (LNR), as the ratio of metastatic lymph nodes to the total lymph nodes harvested, is a more reliable prognostic factor than the number of metastatic lymph nodes alone (22). This is because the negative lymph node count correlates with survival in more advanced cases (23).

The lymph node assessment can influence staging

The factors that may influence the final lymph node staging may be related to: patient (specimens of older patients have usually fewer nodes) (24), tumour, histopathology and surgery.

Histopathological examination is one of the most important factors in determining lymph node staging. Palpation, dissection and treatment of the surgical specimen are all important factors (25). Normally only one section of each lymph node is studied, which can sometimes not be representative. The analysis of multiple sections of the lymph node would lead to an upstaging of the disease, but this is not practiced due to an increase in cost and time of work (26).

Most lymph node metastases occur in small lymph nodes (<5 mm) (27) which are also the most difficult to palpate on histopathological examination. Large lymph nodes may be the site of reactive hyperplasia indicating an active host response and better prognosis (28).

Lymphatic mapping methods, such as indocyanine green (ICG) fluorescence detection of sentinel lymph nodes and modified lymphatic mapping (using India ink), allow the identification of one or more lymph nodes that are studied more intensively ("ultrastaging"), also using immunohistochemistry and molecular techniques (29).

ICG fluorescence-guided sentinel lymph node biopsy (SLNB) in colorectal surgery can be used to adapt the extent of lymphadenectomy, reduce intraoperative risks and postoperative complications. SLNB may play a role especially in early pT1 tumors resected endoscopically. In this case a SLNB could be performed laparoscopically just to evaluate the sentinel nodes and eventually carry on the colonic resection with limphadenectomy. Unfortunately, however, it has been seen that these mapping techniques are not very reliable. Limits of the SLNB are false negatives, skip lesions and sensitivity in identifying the sentinel node (96% detection rate) (15,30,31).

The one step nucleic acid amplification (OSNA) is a quantitative molecular technique that uses reverse transcriptase and polymerase on nucleic acids extracted from fresh lymph nodes to recognize micro and macrometastases. It is usually used for sentinel lymph node analysis (32).

D2 versus D3 limphadenectomy: which one should be practiced?

CME with CVL seems to be more oncologically effective in the most advanced stages of the disease compared with the standard technique (pre-CME or D2): locoregional 5-year recurrences remained below 3% for stages I and II, while for the stage III an improvement in recurrences was seen falling from 14.8% to 4.1%. An improvement was also found in cancer related 5-year survival (79% *vs.* 90%), but the overall survival (OS) rate did not improve significantly (33).

In the Hohemberger *et al.*'s study the cut-off for convenient harvesting was detected at 28 lymph nodes: if more than 28 lymph nodes were removed the cancer-related

5-year survival improved by 5.6% (from 90.7% to 96.3%) for the N0-patients and by 7.1% (from 64.6% to 71.7%) for the N+ patients (the latter group was not statistically significant) (2).

However, these results are certainly not without limits. In fact, in this study patients with non-R0 surgery and surgical mortality (for long-term results) were excluded and the role of adjuvant chemotherapy was also unclear (34).

In the systematic review by Killeen *et al.* the exclusion of the results of the study by Hohenberger *et al.* led to a disease-free survival (DFS) rate of 71.9% for CME with extended lymphadenectomy, similar to that described for non-CME procedures (35,36).

Some studies show that the number of retrieved lymph nodes is an important prognostic variable especially in stages II and III of the RCC.

The study by Kotake *et al.* showed that the 5-year OS improves by 6.4% for stage II and by 8.8% for stage III of colon cancer in the subgroup with the number of lymph nodes removed ≥27 compared to the subgroup with ≤9 lymph nodes removed (37).

A retrospective study analyzed the impact of D2 and D3 lymphadenectomies for pT3 and pT4 colon cancers finding a better OS in patients experiencing D3 lymphadenectomy (38).

Other studies have also reported advantages of extensive lymphadenectomy in terms of DFS, especially for the early stages of the disease (39,40). However, these studies present some data that are difficult to interpret.

In the study by Bertelsen *et al.* specimens from traditional pre-CME surgery were compared with those from CME: the quality of the mesocolic surgical plan, the rate of R0 resections and the risk of complications did not change much (41). Evidently the surgeons who participated in this study performed a right hemicolectomy with mesocolic excision according to the anatomical planes and a fairly high ligation of the vessels already before the birth of CME with CVL.

The 90-day postoperative mortality was seen to be 1.3% higher during D3 lymphadenectomy compared to the classical technique (6.2% *vs.* 4.9%). Intraoperative and postoperative complications are more frequent with D3 lymphadenectomy. Injuries to other organs are 5.5% more frequent during the CME and D3 limphadenectomy; the most common are injury to superior mesenteric vein, spleen and duodenum. Postoperative complications rates of sepsis and respiratory failure are greater in extended lymphadenectomy (42,43).

Another complication of D3 lymphadenectomy is a lesion of the superior mesenteric nerve plexus. It has been seen that this could lead to an increase in bowel frequency, without however affecting the quality of life (44).

From the above it is clear that the data available to us today are not sufficient to prefer one type of lymphadenectomy over another in right hemicolectomy. Surely the number of harvested lymph nodes correlates positively with the prognosis.

Currently, two prospective trials are in progress that will give us more results on the medium- and long-term outcomes of the D2 and D3 lymphadenectomies compared.

RICON is a randomized controlled trial that aims to compare D2 lymphadenectomy and D3 lymphadenectomy in right hemicolectomy for RCC. The primary outcome of this study is 5-year survival and secondary outcomes are morbidity, mortality and 5-year DFS. The study started in 2017, will be completed in 2025 and should clarify which technique is preferable for the RCC (45).

Another randomized controlled trial (RELARC protocol) started in 2016 and compares laparoscopic D2 lymphadenectomy with a wider lymph node excision. This study will last 7 years and should clarify whether there are benefits of a more extensive lymphadenectomy in laparoscopic right colon surgery in terms of 3-year DFS, 3-year OS, complication rates, perioperative mortality rates, and rates of positive central lymph nodes (station 3) (46).

Lymphadenectomy in minimal invasive right hemicolectomy

It has been a long time since laparoscopic right hemicolectomy with standard D2 lymphadenectomy is safely performed (47).

There are two ways to practice laparoscopic right hemicolectomy: the medial-lateral approach is recommended as it better respects the criteria of "no touch" resection, ligation of the vessels at the origin and progression of dissection in the medial-lateral sense, with respect to the latero-medial approach in which the section of the ileum and the colon is provided first and then performed the vascular time (21,43).

Several studies in recent years tried to compare the laparoscopic and open D3 lymphadenectomy for colon cancer in terms of quality of the specimen, oncological outcomes and technical feasibility (48).

There would appear to be no difference between surgical specimens from open and laparoscopic CME with CVL in terms of distance between tumor and colon wall to vessel ligation for right colon tumors (49,50).

Instead, differences were found on transverse and hepatic flexure cancer specimens in terms of anatomical piece quality and collected lymph nodes. In the study of Gouvas *et al.* the lymph nodes collected were on average 46 with the open technique and 39 with the laparoscopic technique (49).

The study by West *et al.* shows that laparoscopic surgical specimens have a significantly lower number of lymph nodes compared to the open ones (18 *vs.* 32) (50).

Comparing the results of different studies in terms of lymph node collection it is evident that the number of lymph nodes harvested by the laparoscopic D3 lymphadenectomy technique practiced in the most of the studies is in each case lower than the number of lymph nodes harvested by Hohemberger *et al.*'s open technique (43,51,52).

Considering the procedure practiced at Erlangen as a CME-CVL with a good quality D3 lymphadenectomy, these studies are evaluating the laparoscopic feasibility of a technique that is perhaps a high quality D2 lymphadenectomy. We want to stress that the D3 lymphadenectomy would require the Kocher maneuver and a collection of lymph nodes at the origin of the superior mesenteric artery and vein.

However, analyzing the studies before 2009, we can notice that with the standardization of CME there has been a change of practice towards a more accurate hemicolectomy with an increased number of harvested lymph nodes (47).

The long-term oncologic findings between open and laparoscopic hemicolectomy with D2 lymphadenectomy are comparable (respectively 3-year DFS 76.2% *vs.* 74.2% and 3-year OS 84.2 *vs.* 81.8%) (47), and appear to be lower than those had with D3 lymphadenectomy.

Instead, data on long-term oncological results between open and laparoscopic D3 lymphadenectomy are controversial: not all studies were able to prove the non-inferiority of laparoscopy compared to open (53).

However, even in terms of oncological findings, D3 lymphadenectomy, whether practiced open or laparoscopically, would seem to lead to better overall results (53-55).

Several studies have demonstrated the technical feasibility of laparoscopic hemicolectomy with extensive lymphadenectomy. Both open and laparscopic techniques would seem to have the same results in terms of postoperative mortality and morbidity, with a reduction in terms of wound infections, intraoperative blood loss and length of hospitalization, and an extension of surgical time in patients operated laparoscopically (48).

CME can also be practiced with robotic technique, leading to oncological results similar to laparoscopic one (DFS was 85% *vs.* 83% and 5-year OS was 77 *vs.* 73 months respectively). The robotic technique would seem to facilitate the performing of the operation, leading to a lower conversion rate (56).

Conclusions

Terminological, geographical and technical differences about lymphadenectomy for RCC resection have led to a state of lack of clarity on this topic.

Currently the European and American guidelines recommend the removal of a minimum number of 12 lymph nodes while the Japanese guidelines suggest modulating lymphadenectomy according to the stage of the disease.

D2 lymphadenectomy can lead to downstaging due to several physiopathological mechanisms: micrometastases, "stage migration" and "skip metastases".

The lymph node assessment, together with surgery, plays an important role in staging and treating patients with RCC, risking to understage the disease as well.

Furthermore, the total number of collected lymph nodes correlates with survival.

Current evidence shows that a more extensive D3 lymphadenectomy can lead to better oncological results in terms of DFS and OS especially in more advanced stages (II and III).

The minimal invasive technique for D2 lymphadenectomy in right hemicolectomy would seem to lead to similar oncological results compared to the open one. Data on oncological results of mini-invasive D3 lymphadenectomy are controversial and require more study to prove its effectiveness and safety.

Two randomized controlled trials are ongoing (RICON and RELARC) and should clarify whether there is an actual cancer benefit in practicing a more extensive lymphadenectomy in right hemicolectomy.

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