

LYMPHADENECTOMY IN COLORECTAL CARCINOMA: REVIEW OF THE LITERATURE

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Abstract: Soon we will be able to stage patients without needing to remove the primary tumour and surrounding lymphatic tissue. Soon we will be able to predict which primary tumours have a predisposition to metastasize and where they will metastasize. Colon and rectal cancer continue to be among the highest incident solid tumours in males and females. In order to define the role of lymphadenectomy in colorectal carcinomas, the literature of past 20 years and the historic publications were reviewed. Special attention was given to statistical relevance, survival, surgical therapy, recurrence rates, lymphadenectomy, and which operation is the best to treat colorectal cancer. The guidelines recommend the radical en block resection of the tumour bearing bowel with central ligation of its vessels, although evidence supports this is limited. In colorectal cancer surgery, the systematic lymphadenectomy of the lymphatic drainage also the arterial blood supply are included in resection. The extent of intestinal resection is determined from the lymphatic dissection. The bowel resection is depending on the tumour depth invasion (pT). – a 5-10 cm resection margin proximally and distally. The lymph node status (pN) is one of the most important prognostic factors. The total number of lymph nodes can be influenced by the surgeon, patient and the pathologist. New studies exist, which show that only small subgroups of patients receive a prognostic benefit from radical lymphadenectomy and because we cannot yet identify these patients pre- or intraoperatively, we continue to perform radical lymphadenectomy. The role of the sentinel lymph node (SLN) is yet unclear.

Cuvinte cheie: cancer colorectal, metastaza în ganglionii limfatici, limfadenectomie

Rezumat: În prezent suntem în posibilitatea de a stadializa pacienții fără să fie nevoie de îndepărtarea tumorii primare și ridicării țesutului limfatic. Suntem deasemenea capabili să prevedem modul în care tumora primară este predispusă pentru metastazare și unde va metastaza. Cancerule de rect și de colon continuă să aibă printre cele mai mari incidențe dintre tumorile solide la femei și bărbați. Pentru a defini rolul limfadenectomiei din cancerule colorectale, a fost revăzută literatura de specialitate din ultimele două decade, precum și istoricul publicațiilor. O atenție specială s-a acordat prelucrării statistice, a relevanței acesteia, a supraviețuirii, terapiei chirurgicale, procentului de recidivă, limfadenectomiei, și în ce fel intervenția este cea mai bună metodă de a trata cancerul colorectal. Ghidurile terapeutice recomandă rezecția radicală în bloc a tumorii în segmentul de intestin aferent și liganții vaselor sale centrale. În chirurgia cancerului colorectal, limfadenectomia sistematică a lanțului limfatic de drenaj aferent de la tumoră, și luat de-a lungul trunchiurilor arteriale de suplulare vasculară, sunt incluse în rezecția tumorii. Întinderea rezecției intestinale este determinată de disecția limfatică. Rezecția intestinală este dependentă și de profunzimea invaziei tumorale (PT), în general 5 – 10 cm fiind necesare distal și proximal de tumoră. Starea nodulilor limfatici (PN) este unul din factorii cei mai importanți. Numărul total de NL poate fi influențat de operator, bolnav și patologul examinator. Studiile noi existente, arată că numai un mic subgrup din pacienți beneficiază de limfadenectomia radicală, și datorită faptului că astăzi nu putem identifica această categorie de bolnavi, în pre și intraoperator, continuăm să efectuăm limfadenectomia radicală. În prezent nu este încă foarte bine definit și definitiv rolul nodulului limfatic santinelă (NLS).

The exact role of lymphadenectomy (LAE) remains uncertain mainly due to a lack of prospective randomized data and controversy on the usefulness and the extent of LAE persist and validation of the existing literature is difficult because the terminologies are different and the statistical relevance of the publications is unclear.(1,2,3,4)

There are many retrospective and prospective randomized trials with statistically significant results on survival and rate of local and distant recurrence.

Resection of the colorectal cancers should be performed with a “no-touch” technique, because past experience has shown the risk of dissemination of the tumour cells into the blood, in case of intraoperative tumour manipulation.(5,6)

Rationale for LAE in Surgery for Colorectal Cancer.

The poor survival, locoregional recurrence after the colon-rectum resection is in correlation with the presence of acute residual tumours or undetectable micrometastasis within the lymphatic system in the mesocolon, mesorectum and the para-aortic nodes.(7)

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At least 85% of cases with resection margin involvement by tumour itself, by node metastasis develop local recurrence.(8,9)

The aim of LAE is to remove all potentially positive node, because, the lymph node status (N), the presence of M (metastasis), and the residual tumour status (R) is one of the most important prognostic factors.

A correct staging of the tumour needs a performed lymphadenectomy, which leads to the indication of adjuvant therapy in stage III colorectal cancer.(10) Resection of lymphatic tissue is the treatment of choice since the intra-operative assessment of malignant involvement versus inflammatory changes by the surgeon is concrete in only 50% (11), and preoperative investigation are accurate in only about 84%.(12)

In 1982 Bill Heald introduced the technique of total mesorectal excision (TME).

In this technique the mesorectum is complete removal with preservation of the mesorectal fascia "boly plave". This technique preserve the autonomic nerves and remove completely all regional lymph nodes.(14) In rectal cancer surgery the circumferential resection margin, which is defined by the mesorectal fascia corresponds the "circumferential" margin of lymphadenectomy.(14)

Heald et al. demonstrated the influence of TME in local recurrence rates with 4,5% local recurrence in 470 stage II-III rectal cancer patient, who underwent operation between 1987 and 2010.(15) Local recurrence rates were 2% in UICC stage I 4% and UICC stage II, and UICC stage III.

Because several studies have shown that mesorectal tumor deposits do not occur more than 4 cm distal to the tumor, partial mesorectal excision provides adequate oncological safety in proximal third rectal cancer.(16,17)

The German Rectal Cancer Study Group has an multicenter trial which examines the impact of partial mesorectal excision compared to TME in rectal cancer of the proximal third (SAST-05 trial. Lymph node metastases can be found even in the lowest part of the mesorectum of the middle or lower third of the rectum.

The deep anterior resection must include a TME up to the muscular pelvic floor.(18,19)

Rectal cancer metastases in the proximal dimension to the root of the inferior mesenteric artery.

A review by Lange et al which examined 23 published articles came to the conclusion that insufficient evidence exists to recommend high tie ligation of the inferior mesenteric artery as the standard procedure and the high tie decreased the innervations of the autonomous nervous system.(20) The authors concluded that low tie was less invasive.(20)

Patients without lymph node metastases or with low number of perirectal lymph node metastases do not need high tie ligation with resection of the central lymph nodes (N3), because these central lymph node do not contain macro or micrometastases, and therefore probably the only patients who will benefit from high tie ligation with central lymph node dissection are those with a real border of lymph node metastases at the central lymph nodes.

A meta-analysis published by Georgian et al in Lancet oncology in 2009 reviewed 20 studies with 5.502 patients about performance of lateral (extended) lymphadenectomy in rectal cancer, showed clearly no survival benefit, no reduction of the rate of distal metastases after extended lymphadenectomy.(21)

Lymph node metastases in colon and rectal cancer patients.

The anatomical studies carried out by Clogg and Jamiesan and Dobson provide important information about the

usual pattern of continuous (stepwise) lymphatic tumour spread to the epicolic, paracolic, intermediate and central nodes in colonic cancer. The incidence of "ship" metastases of the emergency of the inferior mesenteric artery (IMA) in sigmoid or rectal cancer varies from 1 to 17%.(7,22)

In colorectal cancers the lymphatic spread an dissemination follows anatomic roles, with uni or bidirectional drainage of the lymph according to site of tumour, with ship metastases in 3% of cases.(23)

In colorectal cancers the lymph node metastases are correlated with the tumour type, the histological grade of differentiation, the depth of tumour invasion (pT) and the presence of lymphatic vessels invasion.(24)

In colorectal cancer patients, the presence of lymph node metastases (N+) ranged from 2% to 17% for pT1 cases.(25)

In pT2 tumours the risk of N+ increases from 10% in a low risk tumours, to 45% in a high-risk situation, and for pT3-pt4, this risk range from 27% to 77% in high risk cancers. Therefore, only in pT1 low-risk colorectal cancer is indicated a local surgery without radical lymphadenectomy.(24,25)

In the publication of Derwinger et al. about the role of stage migration in colorectal cancer and its relationship to improved lymph node assessment, they observed a trend in stage migration from stages I/II toward stage III, and in addition, the number of assessed nodes, had an impact on survival in stage II.(26,27)

Importance of the total number of resected lymph nodes.

At present, pathologic staging of colon and rectum cancer, remains the only basis for establishing prognosis.

Several publications have described the prognostic impact of the number of resected lymph nodes in colorectal cancer.

Tagliacozzo et al. support and extension of the routinely performed mesenteric lymphadenectomy in right hemicolectomy reaching beyond the origin of the superior mesenteric vessels on the dorsal aspect of the mesocolon.(28)

The results of the operations were statistically not significantly better compared to conventional hemicolectomies.(29)

Vatter et al. examined the relationship between prognosis and the number of lymph nodes examined in stage II.

Derwinger et al. compared two 5-year period and found a significant increase in the number of tumour- infiltrated lymph-nodes, and a trend in stage migration from stage I/II towards stage III. With these observations the study contributed to an increase in the number of cases with indication for adjuvant chemotherapy. Derwinger found that the number of assessed nodes had an impact on survival in stage II.(26,27)

Current guidelines recommend that 12 lymph nodes should be resected and evaluated for adequate tumour staging in colorectal cancer.(28-33) The definition of the extent of LAE (lymphadenectomy) or lymph node dissection in surgical treatment of colonic cancer varies significantly, while for some authors "wide lymphatic excision" means extended colonic resection only to others in means, complete retroperitoneal clearance of all lymphatic tissue form as high as the inferior pancreatic border down to the pelvic brim. Distinction has to be made between mesenteric and extramesenteric LAE. The same confusion exist in the terminology of pelvic lymph nodes dissection in rectal cancer creating an almost incomparable variety of operation and clinical trials.(34-37)

Total mesorectal excision (TM)

Heald et al. (14), Scott et al. (38) published TME, a new operation for rectal cancer, based on evidence of isolated

metastase with the mesorectum distal to the primary tumor. In 50 consecutive patients with TME and radical proximal lymphadenectomy performed by ligation of the IMA (inferior mesenteric artery), 1 cm off the aorta, and ligation of inferior mesenteric vein 1 cm from splenic vein, but without extramesenteric "preaortic strip", were no locoregional recurrence after 2 years but 8% of liver metastases and with significant complication, on 18% rate of anastomotic leakage was noted.

The publications from Mac Farlane et al. (39), and for others excision of mesorectum as a distinct lympho-vascular entity minimized the rate of local recurrence even when the lateral resection margin was tumour infiltrated histologically.(40-44)

The present status of the lymph node ratio in prognosis and survival in colorectal cancer patients.

Berger et al. were the first who published the high prognostic impact of the lymph node rate (LNR) in colon cancer.(45)

The LNR is defined as the proportion of tumour-infiltrated LN compared to the total number of resected LN (lymph-nodes).

$$\text{Nr N+} / \text{Nr NL totali}$$

Berger et al. used the data of the intergroup trial 0089 of adjuvant chemotherapy for stages II and III colon cancer patient (3411 cases). In this study with multivariate analysis, the LNR was independent prognostic factor for overall survival and disease free survival in patients with more than 10 resected LN in the specimen. This result we have in our experience with 344 resected colorectal cancer and with histopathological examines of number of lymph nodes examined in colorectal specimens.(46,47)

DeRidder et al published the largest series, with 26181 patients with stage III disease from the SEER database.(48) They used statistical methods to identify 0,4 as the LNR with the highest prognostic discrimination, and say that the lymph node ratio was an independent prognostic factor very interesting was that in the studies of Berger and DeRidder et al to, the medium number of resected lymph nodes was low, with 10 and 11 respectively. Wang et al. (33) used the SEER database, to examine 24.477 patients with stage III colon cancers to see whether the total number of lymph nodes is an independent prognostic factor often adjusting for LNR. In this study patient with 12 or more resected lymph nodes had a better rate of survival than that with fewer than 12 resected lymph nodes. Very interesting was that patients with 12 or more resected lymph nodes had a significantly worse survival rate than those with fewer than 12 resected lymph nodes in patients with a LNR greater than 0,25.

Derwinger et al examined the prognostic impact of LNR in stage IV colorectal cancer (26,27) and found that the LNR is a prognostic factor in stage IV colorectal cancer, and can be used to stratify stage IV into different prognostic groups. The studies from Parl et al., Frederique et al, and other present studies confirmed that, the lymph node ratio is the most significant prognostic factor for survival in patients with resected colon and rectal cancer.(49-59)

Bowel resection margin and ligation level of the primary (central) artery in colon cancer, and the level of ligation of the IMA (inferior mesenteric artery), in rectal or sigmoid cancer.

The IMA (inferior mesenteric artery) can be ligated in surgery for rectum and sigmoid cancer just below emergency of the left colic artery, this is a "low ligation" or one centimetre below the origin of the IMA is the high ligation.

In current guideline for colon cancer the en-bloc resection involving a systemic lymphadenectomy by ligation of primary feeding artery, and resection the proximal and distal bowel with 5-10 cm bowel margins is considered.

Toyota et al. examined the extent of lymph node dissection for right colon cancer.(60) In this study in most of the curative resection for right colon cancer metastases to epiploic and paracolic nodes were located not more than 10 cm proximally and distally from the macroscopic margin. Less than 1% of positive nodes were located further than 10 cm from the macroscopic margin of tumor. The central nodes were infiltrated in 3,2-3,5% of cases.

In as Experience with intraoperative lymphography in digestive cancers (more than 170 cases), the skipmetastases in right colon cancer, special in transverse colon cancer, represent a real problem about extension of limit of the bowel resection.(61)

In the publication of Hida et al. (62), with 164 patients treated with colon cancer, the authors found for pericolic spread that the proximal and distal distance than the primary tumour to a metastatic nodes was 2,5 cm in pT1 tumours, less than 5cm in pT2, and less than 7 cm in 97% of pT3 and in 93% of pT4 tumours.(62)

In this study, for control spread the rate of spread to control nodes was 0% for pT1 and pT2, 15,4 for pT3 and 22,2% for pT4 tumours.

After this result, Hida et al (62) proposed that central node dissection not required in pT1 and pT2 tumours. The resection of the proximal and distal margin should be performed with a 3 and 5 cm margin in pT1 and pT2 tumours. But in pT3 and pT4 tumours, central node dissection should be performed with proximal and distal 7cm margins.

In an other publication, Lavemitsu et al (63) found that only 1,7% of 11888 patients had tumour infiltrated N+ of the central nodes along the root of the IMA (lymph node station 254 according to the Japanese classification). In the opinion the benefit of routine use of high ligation was low (1,7 and 0,7% of patients with sigmoid rectal cancer are cured by high ligation of the IMA).

The systemic review published by Lange et al (64), found 23 articles that evaluated the colon-rectum cancer patients and concluded that the literature provides insufficient evidence to support high tie as the technique of choice. The low tie of ligation of MAI, is anatomically less invasive with respect of circulation and autonomous innervations and should be the preferred method, the high tie has been proven to decrease perfusion and innervations of the proximal bowel segment of anastomosis.(64-67)

Conclusions:

The extent of lymphadenectomy in rectal cancer is been defined by mesorectal fascia (Henle). The lymph node status, the lymph node ratio, and the circumferential margins are important prognostic factors in rectal and colon cancer.

Lymph node status is a most important element in colorectal cancer staging and selecting for treatment and the lymphadenectomy most standardized and radical.

The lymph node ratio can be used for clinical trials evaluating the benefits of adjuvant chemotherapy after curative resection of rectal cancer.

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