

LEVEL OF VASCULAR LIGATION AND ASSOCIATION WITH ONCOLOGICAL EXPEDIENCY IN SIGMOID AND RECTAL CANCER

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ABSTRACT

INTRODUCTION: The techniques and oncology feasibility of high vascular ligation of the inferior mesenteric artery along with their varieties – low tie (LT) and high tie (HT) techniques in left-sided colon and rectal cancer, were described more than 100 years ago by Miles and Moynihan. However, the relationship between the level of vascular ligation and the microperfusion of the proximal anastomosis segment, on the one hand, and the volume and quality of lymphatic dissection, on the other, are the subject of numerous clinical trials and discussions. The vegetative nerve spare in the different approaches is also included in a consideration. Despite the well-established modern standardization in conventional and laparoscopic left colon and rectal cancer surgery, some surgeons still do ligation at the a. rectalis superior level in rectal cancer, which contradicts modern oncology principles.

MATERIALS AND METHODS: Prospective non-randomized comparative cohort study of patients from the Department of Surgery in Alexandrovska University Hospital with cancer of the sigmoid colon or rectum in clinical stage I-III, operated by an open or laparoscopic approach over a 4-year period, stratified into two groups according to the level of ligation of the inferior mesenteric artery (IMA) and vein - high tie - at the site of the origin (1 cm) from aorta and low tie - distal to the origin of the left colic artery. The comparative indicators included the anastomotic leakage rate, the number of lymph nodes harvested with a metastatic lymph node index, a 3-year disease-free survival (DFS), disease-related survival OS. The follow-up period was 12-48 months.

RESULTS: For the period 2014-2018 a total of 217 patients with cancer of the sigmoid colon or rectum underwent 169 laparoscopic and 48 open surgeries. The distribution was as follows: 69% high ligation compared to 31% low ligation; 52 in an emergency or delayed emergency manner; 58% male and 42% female, mean

age 64±0.8 years; 56% in clinical stage III, 40% in II and only 4% in clinical stage I, relatively evenly distributed in the two target groups. There were wide variations in the number of lymph nodes harvested from the specimen (n = 4 to 22) for both groups without significant differences in the metastatic index. There was no statistically significant difference in the incidence of anastomotic leaks for both groups (3.8% for HT versus 3.0% for LT). With respect to the 3-year disease-free interval, there were

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also significant differences - 81.2% (HT) and 79.4% (LT) and the overall survival rate of 79.1% (HT) compared to 77.2% (LT) with a 72% follow-up coefficient.

DISCUSSION: The findings of this study are broadly consistent with those published so far and analyzed in three systematic reviews - the last one in 2018. This indicates that no statistically significant difference between high and low vascular ligation has been identified for the most important comparative indicators. It is extremely important to discuss several technical issues at present - contemporary problems requiring future high-quality clinical trials: the necessity and means of implementing left colic flexure mobilization in both types of vascular ligation with the lack of standardization; adequate and accurate identification of a correct cleavage plane of the dissection with differentiation of target vascular areas, avoiding erroneous entry into the sigmoid mesentery along with separate ligation of sigmoid vessels - oncologically inappropriate; sequence and level of ligation of the lower mesenteric vein with wide variations; pathoanatomic processing of the specimen with adequate isolation and examination of the removed lymph nodes, respectively adequacy of the pathohistological N-staging as well as the quality of the mesorectal excision; the need for stage control of the microvascular perfusion of the anastomosis segments by ICG fluorescence on the already validated global methods (hence the prevention of anastomotic leaks); progress in the importance and technical feasibility of low tie vascular ligation + perivascular lymph dissection to the IMA origin, and complete mesocolic excision (CME) in colon carcinoma (similar to TME in the rectal), the subject of more and more current studies; the specifics and advantages of robotic surgery of left-sided colon and rectal cancer with respect to accuracy of vascular and lymphatic dissection.

Keywords: *left colon and rectal cancer, vascular ligation level, high tie, low tie*

INTRODUCTION

Modern surgical technique, treating left-sided colon cancer and rectal cancer, has well standardized approaches for different stages in conventional and laparoscopic surgery. The problem of ligation level for inferior mesenteric artery (IMA) is put to discussion, and there is no consensus in the different centers and between the surgeons. The most important prognostic factors of overall survival in patients with colorectal cancer are distant metastases and local lymph node involvement. In accordance with this, in 1908 Miles introduced transabdominal lymph node dissection along the main nutritive vessels as a stage of the standard abdominoperineal resection. He suggested division and ligation of *a. rectalis superior* (SRA) distally to the separation of the left colic artery, the so-called low tie (LT) technique (Fig. 1), and further dissection of the lymph nodes in the distant colorectal segment. The same year, Moynihan was the first to suggest ligation of entire arterial trunk at its origins from the aorta. It included removal of the apical group lymph nodes, situated around it, the high tie (HT) technique (Fig. 2). In the

following years, the HT technique was widely accepted by the surgeons in routine practice.

In fact, level of vascular ligation varies a lot across different surgeons. Daily practice shows that a few of them dissect at the origin of left colic artery (LCA), because of incorrect evaluation of IMA and SRA division level. This leads to terminologically incorrect determination of the arterial ligation site. Lanz Wachsmut focused on that by defining the artery distal to the left colic artery as upper rectal artery, not inferior mesenteric artery (1,2). Most authors use high tie for any ligation on the mesenteric artery, from 1 to 7 cm along, between its origin and the division of left colic artery (2). In 1959 Dunphy suggested a modified procedure by performing LT vascular ligation combined with dissection and excision of the fatty tissue between the aorta and the root of the inferior mesenteric artery, which contains the apical lymph nodes (Fig. 3). This technique appears to be a compromise between the other two (3) and is accepted as standard for good surgical practice.

The process of choosing the site of vascular ligation consists of 3 milestones - oncological, anatomical and technical.

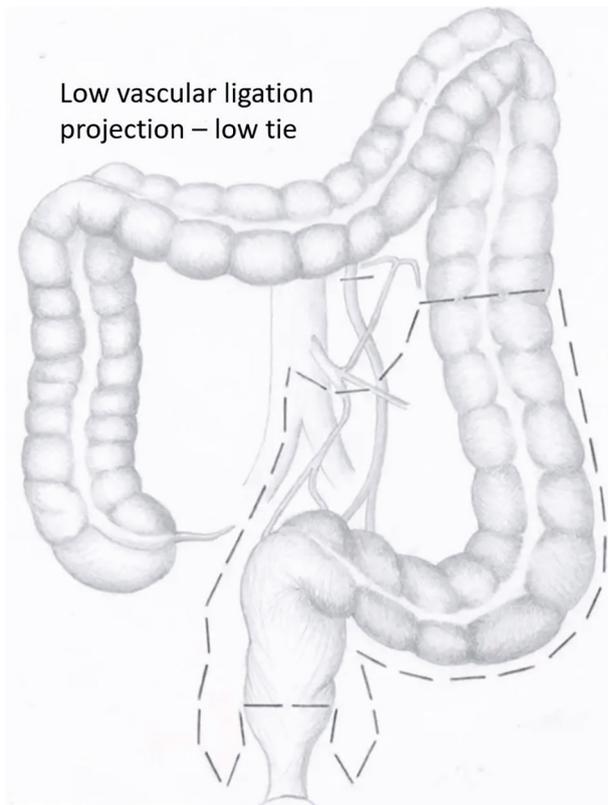


Fig. 1. Low vascular ligation projection – low tie

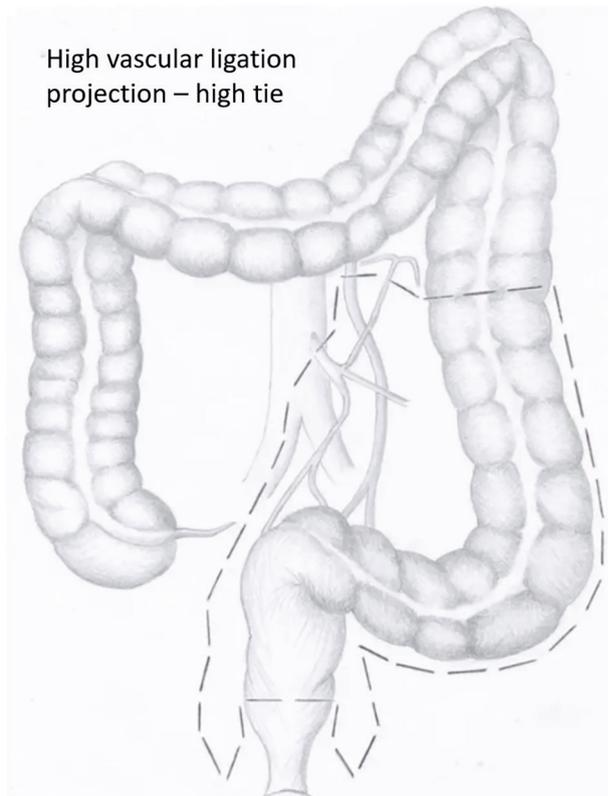


Fig. 2. High vascular ligation projection – high tie

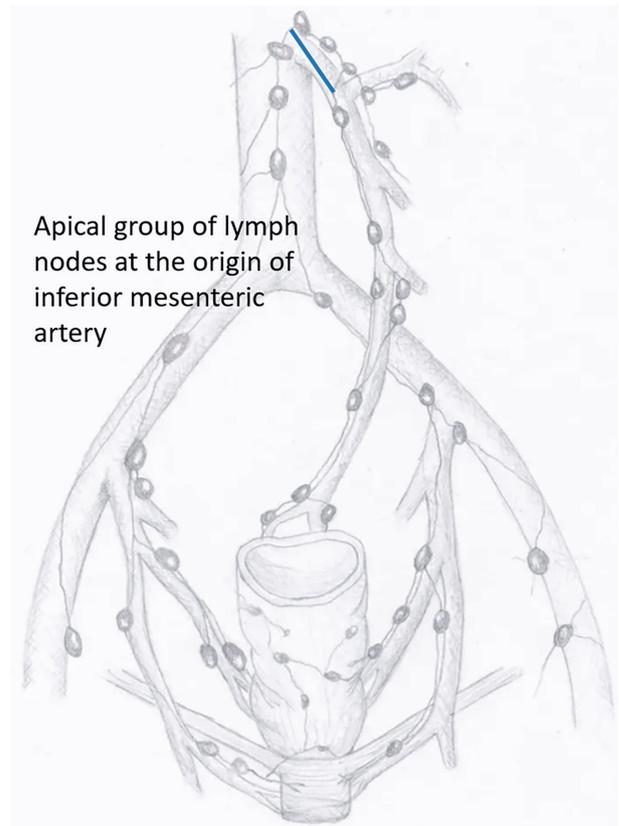


Fig. 3. Apical group of lymph nodes at the origin of inferior mesenteric artery

Oncological Considerations

The HT technique includes a dissection of an apical group lymph nodes situated at the root of IMA. A few studies show a relatively low percent of metastatic involvement of these nodes – 0.3-8.6%, but it is not low enough to be disregarded (4,5,6). Kanemitsu et al. (7) did not find any metastases in the apical group nodes in patients with pT1 rectal and sigmoid tumors, therefore they suggest LT for these types of tumors. HT is to be reserved for patients with positive lymph node involvement. Data from the Japanese Society for Cancer of the Colon and Rectum show the incidence of apical node involvement to be 3.6% in pT3/T4 sigmoid cancer and 5.1% in rectal cancer (8). On the other hand, pN3-positive disease always has poor prognosis, even if HT ligation and lymph node dissection is performed. Variations in lymph drainage also could compromise the advantages of HT - tumors in upper third of the rectum can be drained by lymph pathways following the portal vein leading to isolated metastases in hepato-

duodenal ligament nodes (9). Lower tumors, situated at the proximal part of the rectum can give metastases to the iliac lymph nodes, through lymph pathways located in the lateral rectal ligaments (10). Most of the researches do not show a significant difference for HT and LT, in carcinoma specific survival in rectal cancer patients. Previous studies put forward the role of the removed lymph node count, which correlates to long-term prognosis in colorectal cancer patients. They launched a rule of a minimum of 12 regional nodes removal, evaluated histologically, to be the standard (11,12). The idea is that limiting the dissection by preserving IMA in the LT technique is reducing the amount of removed nodes, only in the context of insufficient LT with preservation of significant parts of the mesocolon and mesorectum. It is the so-called tubular resection - close to the intestine and non-oncological. Removal of more unaffected lymph nodes at the root of IMA does not show better clinical outcomes for the patient (13). Only one research, published in 2017, compares LT to selective sigmoid arterial ligation. The results are equivalent in terms of short-term intra- and postoperative results, but with low statistical and scientific value, because of the data including retrospectively only 27 patients, grouped 2:1 and with a short follow-up period (14). Neoadjuvant radiotherapy is relevant only for local tumor control and downstaging, with no advantage in the prevention of distant metastatic spread (Dutch TME trial) (15). Significance and evidence levels for the HT technique being superior to LT are insufficient to standardize the level of vascular ligation. LT with LND is anatomically less invasive, comparative to HT in terms of oncological prognostic value (8).

Anatomical Considerations - Proximal Part Perfusion of the Intestinal Segment or the Colostomic Segment

Good microperfusion of anastomotic edges is critical for its integrity and in the prevention of anastomotic leakage. Studies show that LT permits adequate blood perfusion of the proximal intestinal segment (LCA + marginal artery of Drummond), while in HT the vascularization of the distal descending colon and the sigmoid colon is determined by the middle colic artery and Drummond marginal artery, which originates from left colic artery. It is crucial for the vitality of proximal intestinal segment. Studies performed by laser Doppler flowmetry show sig-

nificant hypoperfusion of the segment, when HT is performed (16,17). Another prospective cohort study in 2016, also with laser Doppler flowmetry, does not show a significant difference in blood perfusion after HT or LT (18). Hinoi et al. (2013) studied 888 patients with rectal cancer in the lower and middle third of the rectum and found that anastomotic leakage appeared less frequently in patients with preserved left colic artery (19). A higher value scientific research consisting of systematic review and meta-analysis (2015) of 14 studies, with data on 4580 patients, did not show significant differences between HT and LT in terms of anastomotic leak incidence (20). Systemic low blood pressure and hypoperfusion, in the early postoperative period, may lead to low perfusion of the proximal intestinal segment through the marginal artery, despite its mechanisms of volume autoregulation. This is mainly observed in patients with atherosclerosis of the splanchnic vessels and severe cardiovascular comorbidities (21). In some patients lack or insufficiency of the marginal artery can be observed as an anatomical variation (22). In his study S. Tsujinaka estimated a 2.0% incidence of proximal intestinal segment necrosis, with potentially fatal consequences (23). Despite the contradictory arguments, there is no significant evidence in favor of LT to prevent anastomotic dehiscence, except for patients with severe vascular atherosclerosis. This statement was proved by Fujii et al. in 2018, whose study is with the highest evidence value (24).

Autonomic Innervation

Autonomic nervous system preservation during vascular and lymph node dissection (para-aortal truncus of mesenteric plexus, descending in front of the aorta, then merging to form the upper hypogastric plexus) is proven to be crucial for the prevention of urogenital and anorectal dysfunction. In HT there is a possibility of them being damaged or completely severed, that is why they should be identified intraoperatively. Two anatomical researches show that 1 cm below the origin of IMA a vascular ligation is considered safe, without the danger of damaging the nerves (25,26), while another study finds a dense network of autonomous nerve fibers at the 5 cm mark along the artery, starting from its root (27). This further complicates the problem of determining the level of vascular ligation site. Liang and Sato et al. studies show that patients treated with HT have worse

functional outcomes, but there are no unambiguous evidences presenting that the LT technique has better prognosis in terms of intestinal and urogenital functions. This was demonstrated by Matsuda et al., in their Japanese, highly evidential, randomized controlled study, in 2005 (28). An Italian randomized controlled study (HIGHLOW Trial) of 214 patients, published in 2018, reported better results in terms of urogenital dysfunction, with no difference in oncological outcomes and anastomotic leakage incidence, for patients with low rectal resection and LT vascular ligation (29).

Technical Considerations

Along with the ischemia, tension of the anastomosis is proven to be a risk factor for anastomotic dehiscence (anastomotic leakage) (26,30,31). Some authors believe that the HT technique has no alternative in low rectal resections, but only the proximal anastomotic segment is protected against ischemia by the intact LCA-IMA-aorta collateral pathway (30,31,32). Despite this, the ligation of IMA at the lower border of the pancreas provides insignificant elongation of the intestinal segment in LT group. Furthermore, tension-free anastomosis can be accomplished by ligation of the descending branch of LCA (33). Different studies of Pezim and Nicholls (4), Corder et al. (34) did not establish any advantage of LT in providing critical length to the proximal intestinal segment. There is a debate whether routine splenic flexure mobilization (SFM) is necessary to avoid tension at the anastomotic sites in the anterior resection of the rectum, and a discussion on the relation between SFM and HT or LT technique. The reasons are as follows: the technically more difficult procedure during laparoscopic surgery and lack of evidence about its actual effect on the elongation of the intestine; procedure duration; early postoperative complications - anastomotic leakage and other; number of patients who actually need SFM. Cadaveric anatomical researches show that by partial flexure mobilization, a mean of 10 cm of elongation is achieved compared to 28 cm in complete mobilization. The last published research on this subject is from March 2019, by Girard et al., demonstrating elongation of 9 cm in HT, compared to 3-4 cm in LT (35). The Singapore (2008) and Dublin (2007) studies show that an actual necessity of SFM is found only in 25%, respectively 28%, of the patients with anterior resection of the rectum,

and there is equal incidence of anastomotic leakage in patients with HT, with or without SFM. Gouvas N (2014) reports that mobilization of the flexure in HT provides tension-free and sufficient vascularization, without certain effects on early postoperative complications (including anastomotic dehiscence). On the other hand, it substantially increases the duration of the surgery.

MATERIALS AND METHODS

The design of the study is a prospective non-randomized comparative cohort study of patients from the Department of Surgery in Alexandrovska University Hospital with cancer of the sigmoid colon and rectum in clinical stage I-III, operated by an open or laparoscopic approach over a 4-year period. The patients were stratified into two groups according to the level of ligation of the IMA and vein - high tie - at the site of the origin (1cm) from aorta, and low tie - distal to the origin of the left colic artery. Comparative indicators are the anastomotic leakage rate, the number of lymph nodes harvested with a metastatic lymph node index, a 3-year disease-free survival (DFS), disease-related survival OS. The follow-up period was 12-48 months. The data was processed and analyzed by SPSS 18.0.

RESULTS

For the period 2014-2018, 217 patients with cancer of the sigmoid colon and rectum were operated - 169 laparoscopic and 48 conventional surgeries. A total of 52 (24%) of the operations were an emergency or delayed emergency. Patients were divided into two groups - group A with HT vascular ligation and group B with LT, without randomization, based on the operators' expertise. In group A there were 149 patients (69%) with HT, compared to 67 (31%) in group B with LT. Out of the sample 58% were men and 42% were women, the mean age was 64 ± 0.8 years. A total of 56% were in clinical stage III, 40% in clinical stage II and only 4% were clinical stage I, relatively equally distributed in the two groups (mean for group A - 0.4, and for group B - 0.3). Wide variations in the number of the isolated lymph nodes were pathohistologically detected in the submitted specimens - 4 to 22 in both groups, with no statistical difference in the metastatic index. In group A there were 6 anastomotic leakages (3.8%), and in group B

this complication was detected in 2 patients (3.0%), with no significant statistical difference. In the follow-up period and the 3-year disease-free interval there were also no significant differences - 81.2% in group A (HT) and 79.4% in group B (LT). The overall survival was 79.1% (group A) compared to 77.2% (group B) with an actual follow-up coefficient of 72% for a period of 12-48 months.

DISCUSSION

In some centers HT vascular ligation is accepted as a rule, in attempt to achieve tension-free anastomosis and better oncological results by removal of the apical lymph nodes in these patients. In other centers LT is a preferred option, based on the absence of significant evidence for a difference in specific oncological survival and more accurate preservation of proximal intestinal segment microperfusion in order to prevent anastomotic insufficiency, also for its lower risk of damage to the hypogastric plexus. Routine performing of HT is still in discussion, because there is no significant evidence of its advantage in proximal intestinal segment elongation and construction of different types of intestinal anastomoses; on proximal segment microcirculation; on early postoperative indicators: colonic ischemia and anastomotic dehiscence; on late oncological results and late functional results.

Splenic flexure mobilization provides elongation of the proximal intestinal segment, but has no proven effect on anastomotic leakage incidence. It increases surgical duration and is in fact necessary in under 30% of the cases. A prospective cohort study shows that LT combined with splenic flexure mobilization provides adequate length for colo-anal anastomosis construction, only in half of the cases (36). In comparison HT ligation allows construction of all types of colorectal anastomoses, while in LT further division and ligation of the descending branch of previously preserved LCA is needed to perform low colorectal or colo-anal anastomosis (33). Selective approach in splenic flexure mobilization might bring advantage to certain patients, depending on the level of arterial and venous ligation, volume of sigmoid resection, the type of colorectal anastomosis (37). LT can be a better option in severely ill patients (including such with cardiovascular diseases).

The submitted results in this study coincide with the results published and analyzed in three systematic reviews in 2018. This confirms the thesis that at the moment there is no significant statistical difference between high and low vascular ligation in terms of the most important comparison indexes. For the contemporary surgical reality of our surgical practice it is extremely important to discuss a few technical considerations - modern problems, demanding future high quality clinical researches with high level of evidence: necessity and approaches to left colic flexure mobilization in both types of vascular ligation, with missing standardization for complete and partial mobilization; adequate and precise identification of certain cleavage planes of the dissection, with differentiation of target vascular areas, avoidance of incorrect invasion to the mesosigmoid, leading to division and ligation of sigmoid vessels, which is oncologically irrelevant; consistency and site of ligation of IMV with wide variations; pathoanatomical processing of the specimen with adequate isolation and examination of the removed lymph nodes, adequate N-staging and quality of mesorectal excision; necessity of microperfusion control of the anastomotic segments through ICG fluorescence according to the accepted one worldwide, up-to-date modalities, and by this - prevention of anastomotic leakage; progress and importance of the technical performance of LT + perivascular lymph node dissection at the origin of IMA, also a complete mesocolic excision (CME) in colonic cancer (analogic to TME in rectal cancer) – a subject to many contemporary studies; specifics and advantages of robotic surgery in left-sided colic and rectal cancers in accordance with the exact vascular and lymph dissection.

CONCLUSION

HT and LT have comparative oncological results. HT should be preferred in advanced cancers, because involvement of the apical nodes is presumed. LT is a method of choice in early stages (T1-T2). LT with apical lymph node dissection is an acceptable contemporary modality for the discussion of vascular ligation level (8,37). At the present moment there is no precise data whether LT has an advantage in terms of prevention of autonomic nervous and urogenital dysfunction. New prospective randomized and highly evidential studies are needed in

order to standardize the procedures in specific clinical situations.

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