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Does high ligation of the inferior mesenteric artery affect the results of surgery for rectal cancer? (a systematic review and meta-analysis)

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ABSTRACT *AIM: to compare methods of high and low ligation of the inferior mesenteric artery (IMA) in relation to early and late outcomes in surgery for rectal and sigmoid cancer.*

MATERIALS AND METHODS: the systematic review performed in accordance with PRISMA practice and guidelines.

RESULTS: eighteen studies (5 randomized clinical trials and 13 retrospective studies) are included in the study. The meta-analysis demonstrated that left colic artery (LCA) preservation significantly reduced the incidence of anastomotic leaks compared with high ligation of IMA (OR = 1.60; CI 1.23–2.10; p = 0.0006). There were no differences in operation time, blood loss, frequency of splenic flexure mobilization, number of harvested lymph nodes, incidence of urinary dysfunction, postoperative hospital stay and 5-year disease-free survival.

CONCLUSION: low ligation of the IMA improves the blood supply to the anastomosis and reduces the risk of anastomotic leakage.

KEYWORDS: *low tie, high tie, rectal cancer, high ligation, low ligation, rectum, leakage, inferior mesenteric artery*

CONFLICT OF INTEREST: *The authors declare no conflict of interest.*

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RELEVANCE

Recently, surgery remains the main method for rectal cancer (RC). Heald R.J. [1] proved that the results of rectal cancer treatment depend not only on the prevalence of the tumor process, but also on the quality of the surgical specimen, according to the concept of total mesorectumectomy (TME). Also, one of the main stages of this surgery is the ligation of the inferior mesenteric artery (IMA), while the question of the level of ligation of the vessel is a subject for discussion. Some authors [2] believe that a high IMA ligation should be performed at the place of departure from the abdominal aorta (Hightie), while improving long–term treatment results. On the contrary, there is an opinion of Seike K. et al. [3] that the preservation of the left colon artery (LCA) is relevant, and low ligation of the IMA (Lowtie) is performed, respectively, blood flow in the intestine being lowered for anastomosis improves. It is important to emphasize that the level of crossing the IMA is not regulated in national clinical guidelines [4], and the decision is made by the operating surgeon, more often due to personal preferences.

AIM

To compare two methods of crossing the IMA, in relation to immediate and long-term results of treatment of patients with cancer of the rectum and sigmoid colon.

MATERIALS AND METHODS

The meta-analysis was performed in accordance with the recommendations of "The preferred reporting items for systematic review and meta-analyses" (PRISMA) [5]. The literature search was conducted in the electronic database of medical literature PubMed for the last 5 years. The key query terms: "low tie", "high tie", "rectal cancer", "high ligation", "low ligation", "rectum", "leakage", "inferior mesenteric artery". Additionally, the search was carried out on the bibliographic data of selected studies in order to identify undiscovered articles during the initial search. The meta-analysis included full-text articles in English, in which direct and oncological results were compared after surgery with high and low IMA ligation.

Statistical Analysis

A statistical analysis was carried out using the Review Manager 5.4.1 program. The total value of dichotomous data is described as a ratio of odds (OR) with a 95% coincidence interval (CI). OR was calculated using the Peto method if one of the values of the bipartite table was 0. Continuous data was described by a non-standardized weighted average with CI 95%. Statistical heterogeneity among the studies was assessed using the χ2-test. Statistically significant heterogeneity was considered at $p < 0.1$ and $I^2 > 50\%$.

Search Results

When compiling queries in the PubMed, 1,753 publications were found. After screening, 38 full-text articles were selected for this meta-analysis. At the next stage, literature reviews and interim results of randomized clinical trials were excluded. As a result, 18 studies were included in the analysis, of which 5 studies were randomized, 13 were retrospective (Fig. 1). Thus, 6,051 patients were included in the meta-analysis, of whom 3,657 had an IMA ligation at the place of ramification from the abdominal aorta, and 2,394 had an IMA ligation distal to the left colon artery.

Quality of Research

Among the randomized studies, the risk of bias was verified, the diagram was compiled using the Review Manager 5.4.1 program (Fig. 2).

All non-randomized studies were analyzed using the Newcastle-Ottawa Scale (NOS) comparative research quality assessment system [6]. High-quality studies were considered to have a score on the NOS scale of at least 6 stars out of 9 possible (Table 1). It should be noted that most studies (10 out of 13) have 7–8 stars.

RESULTS

The operative time did not differ significantly with the ligation of the IMA at the base and with the ligation of the IMA with the preservation of the LCA (Fig. 3) (The mean difference = –5.12; CI –11.22–0.97; $p = 0.10$).

The volume of intraoperative blood loss in patients with high and low IMA ligation had no significant differences (Fig. 4) (The mean difference = –2.94; CI –9.04–3.16; $p = 0.34$). The incidence of mobilization of the left flexure of the colon (Fig. 5) did not differ significantly in both groups (OR = 2.03; CI 0.69–5.98; $p = 0.20$).

When comparing the number of detected lymph nodes in the surgical specimen (Fig. 6), there were no significant differences in patients with high IMA ligation and with preservation of LCA (The mean difference = 0.01; CI –0.82–0.83; $p = 0.99$).

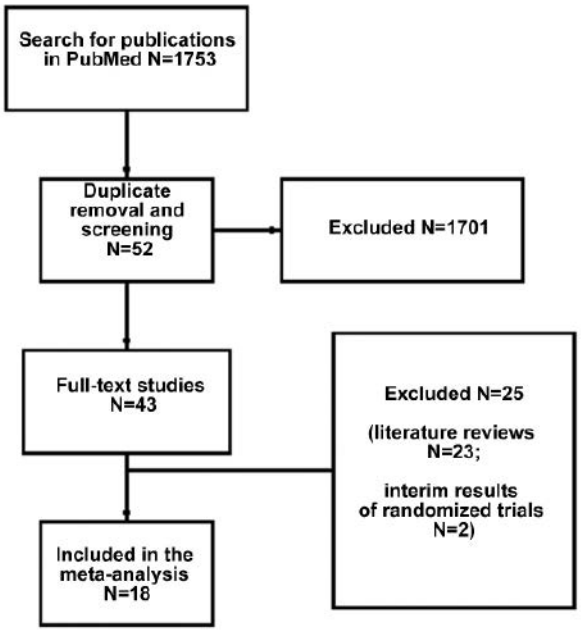

Figure 1. *Block diagram of literature search*

Table 1. *Characteristics of the included studies*

Author	Period	Country	Type	Quality scale	N patients	
					HT	LT
AlSuhaimi, MA [7]	2007–2013	Korea	Retrospective	7	835	378
Chen, J-N. [8]	2017–2019	China	Retrospective	7	235	227
Dimitriou, N. [9]	2009–2014	Greece	Retrospective	6	76	44
Draginov, A. [10]	2002–2018	Canada	Retrospective	7	158	123
Feng, W. [11]	2016–2018	China	**Randomized**	–	47	48
Fujii, S. [12]	2006–2012	Japan	**Randomized**	–	164	160
Guo, Y. [13]	February-December 2013	China	**Randomized**	–	29	28
Kim, C.S. [14]	2011–2015	Korea	Retrospective	6	97	97
Lee, K.H. [15]	2008–2013	Korea	Retrospective	6	51	83
Luo,Yang [16]	2013–2016	China	Retrospective	8	378	236
Luo,Yuwen [17]	2014–2015	China	Retrospective	8	295	221
Mari, G. [18]	2014–2016	Italy	**Randomized**	–	111	103
Matsuda, K. [19]	2008–2011	Japan	**Randomized**	–	51	49
Nayeri, M. [20]	2005–2017	France	Retrospective	8	101	99
Park, S.S. [21]	2010–2013	Korea	Retrospective	7	613	163
Qi, Z. [22]	2013–2014	China	Retrospective	8	116	108
You, X. [23]	2010–2017	China	Retrospective	7	174	148
Zhang, C. [24]	2009–2015	China	Retrospective	8	126	79

When comparing the rate of urinary dysfunction among patients with high IMA ligation and preservation of LCA (Fig. 7), no significant differences were found (OR = 1.23; CI 0.6–2.49; $p = 0.57$).

When studying the rate of colorectal anastomosis leakage (Fig. 8), it turned out that this complication was significantly less common in patients with preserved LCA (OR = 1.60; CI 1.23–2.10; $p = 0.0006$).

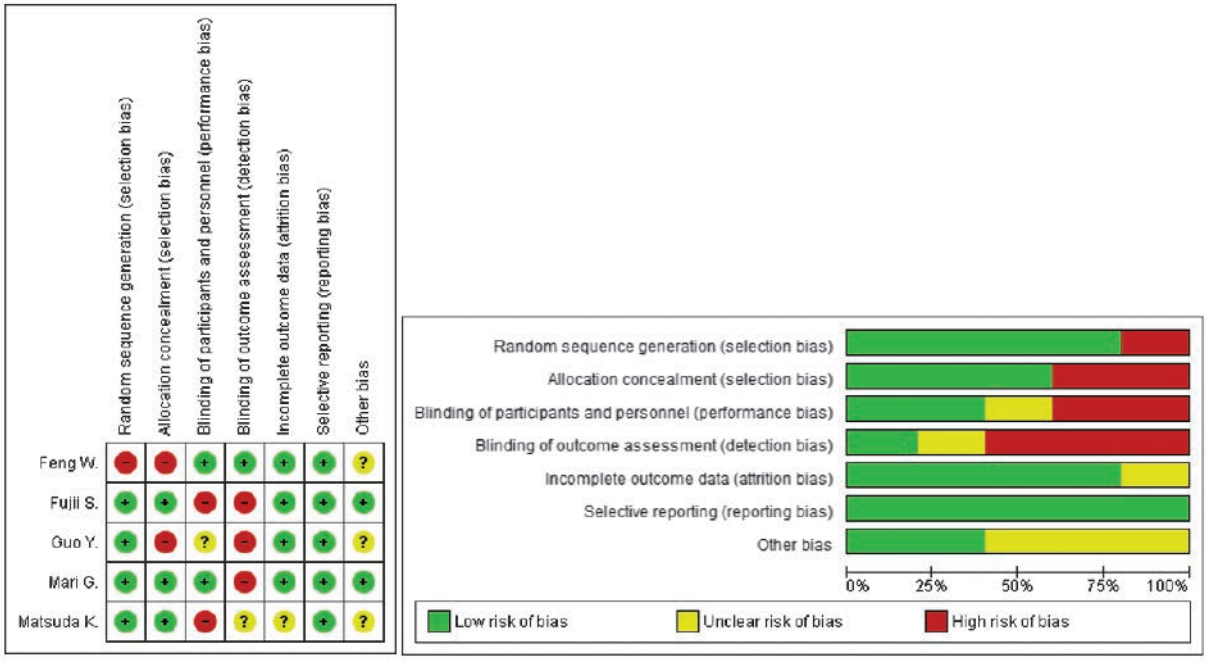

Figure 2. *Assessment of bias risk in studies comparing high ligation and low ligation of IMA*

The number of postoperative hospital-stay (Fig. 9) had no significant differences in the compared groups (The mean difference = 0.41; CI –0.31–1.12; $p = 0.27$).

When studying the late results of surgery, it was revealed that the 5-year disease-free survival (Fig. 10) in patients with high IMA ligation and in patients with preserved LCA did not differ significantly (OR = 0.98; CI 0.82–1.17; $p = 0.81$).

Within the framework of the presented meta-analysis, a sub-analysis was carried out among randomized studies: it should be noted that the rate of AL (Fig. 11) did not significantly differ depending on the choice of the ligation level of the IMA (OR = 1.28; CI 0.82–2.00; $p = 0.28$).

Also, we did not obtain significant differences in the incidence of urinary dysfunction in patients with high and low IMA ligation among randomized trials (Fig. 12), (OR = 1.43; CI 0.53–3.82; $p = 0.48$).

Analyzing the late results, it turned out that the 5-year disease-free survival (Fig. 13) did not significantly differ in patients with high IMA ligation and in patients with preserved LCA when

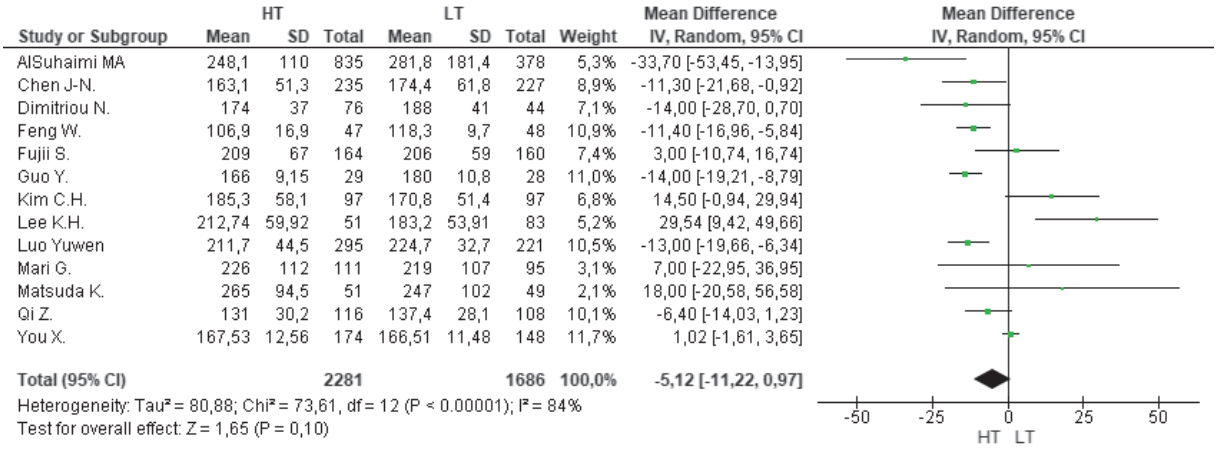

Figure 3. *Operation time*

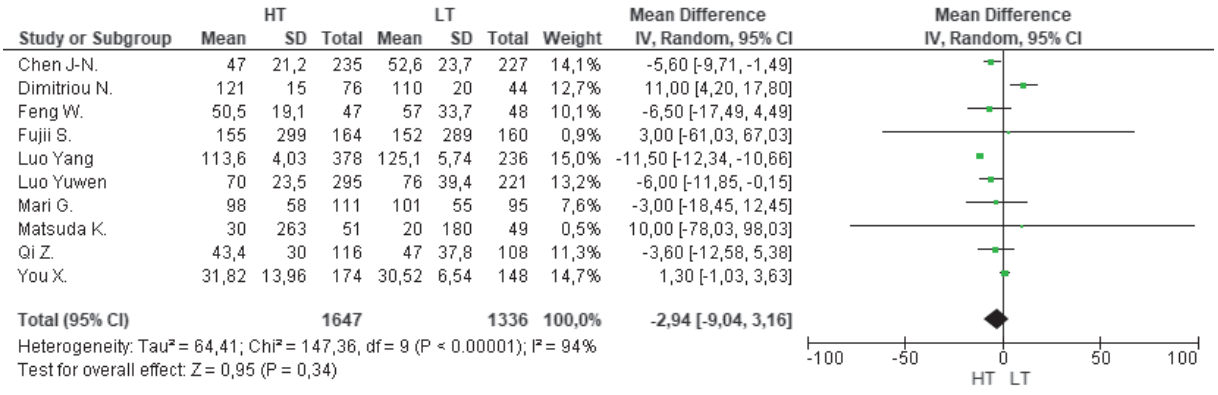

Figure 4. *Bloodloss*

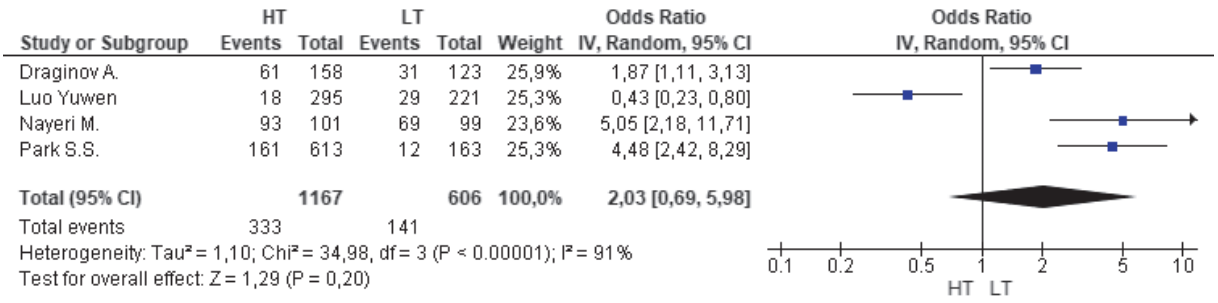

Figure 5. *Splenic flexure mobilization*

compared among randomized trials (OR = 0.78; CI 0.44–1.37; $p = 0.38$).

DISCUSSION

The standard volume of resection for sigmoid and rectal cancer includes removal of a part of the large intestine with a tumor, resection of the mesentery or mesorectum, as well as the ligation of the inferior mesenteric artery [25].

A controversial issue in rectal cancer surgery remains the choice of the IMA ligation level. According to the consensus of the American Society of Colorectal Surgeons of 1999, two methods of ligation of the inferior mesenteric artery are possible: ligation at the base (immediately after the ramification from the aorta), as well as ligation distal to the ramification of the left colon artery — "low ligation" [25]. For the first time, the "low IMA ligation" was proposed by Miles W.E., while the high ligation was proposed by Moynihan, BGA. The both methods of dressing were proposed in 1908 [26, 27].

To date, despite the development and improvement of surgical and stapler technology, the problem of the leakage of colorectal anastomoses is relevant and depends on many factors. There are conflicting data regarding the effect of each of the methods of the IMA ligationon the rate of anastomosis failure. So, Zeng J. in his meta-analysis demonstrated that when cut off the IMA at the place of ramification from the aorta, the risk of anastomosis leakage is significantly higher compared to the IMA ligation with the preservation of LCA (OR = 1.33; CI

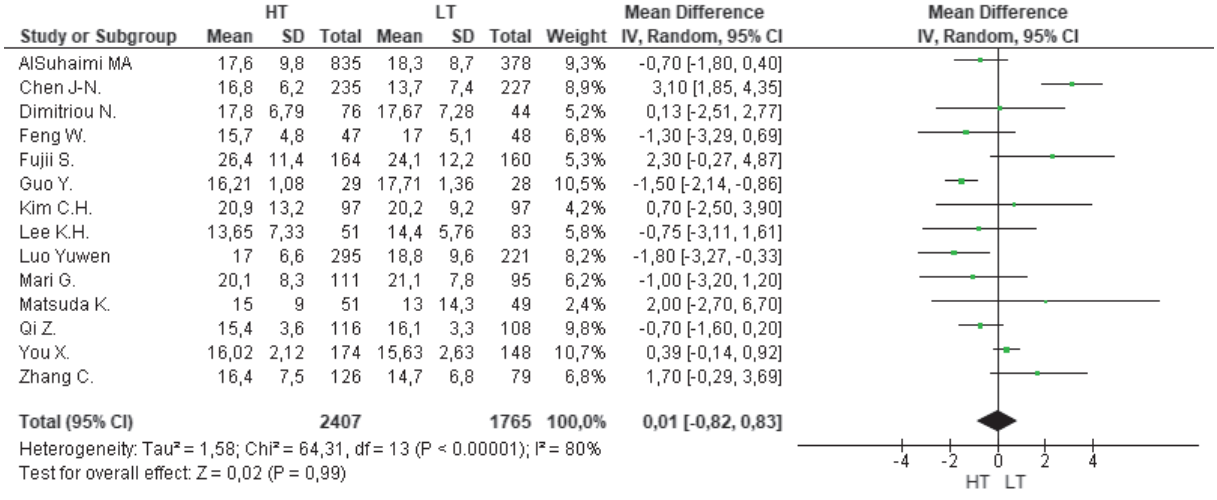

Рисунок 6. *Количество обнаруженных лимфатических узлов*
Figure 6. *Lymph nodes harvested*

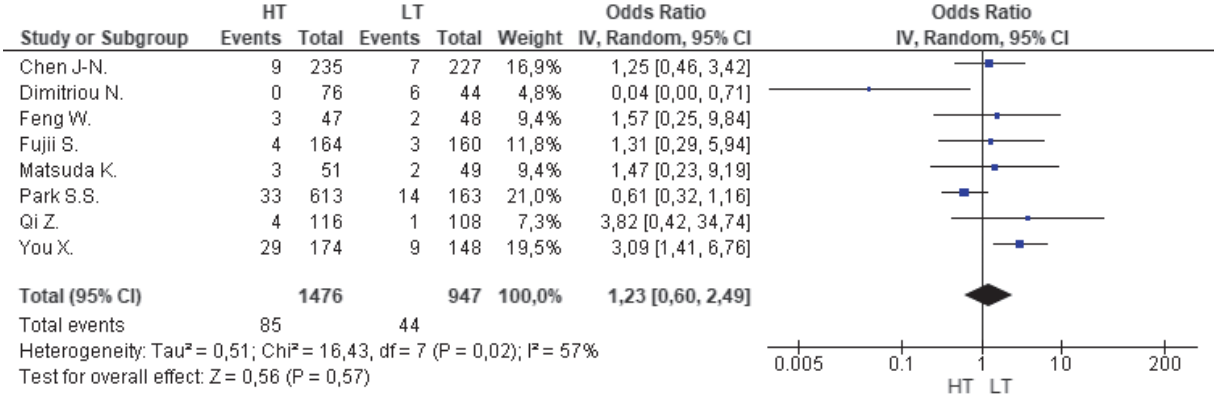

Рисунок 7. *Нарушение функции мочеиспускания*
Figure 7. *Urinary dysfunction*

1.10–1.62; p = 0.004) [28]. However, Rutegard M. provides opposite data that high IMA ligation is not associated with an increased risk of colorectal anastomosis leakage p = 0.946 [29]. The results of the presented meta-analysis indicate that in patients who underwent IMA

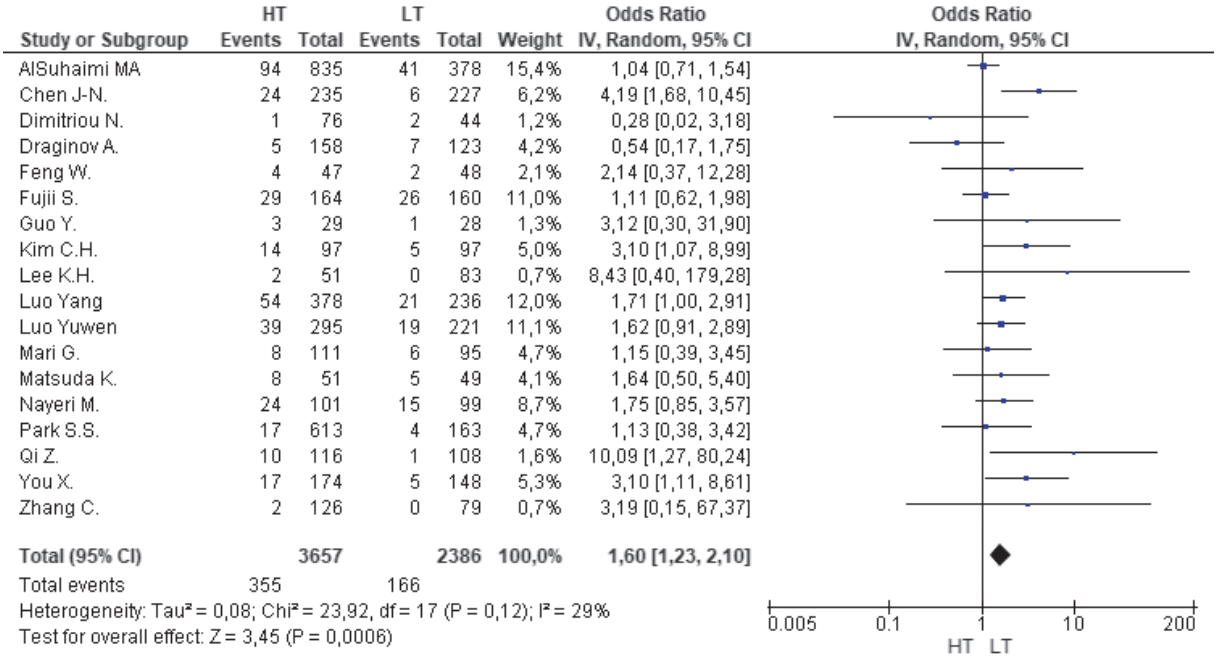

Figure 8. *Anastomotic leakage*

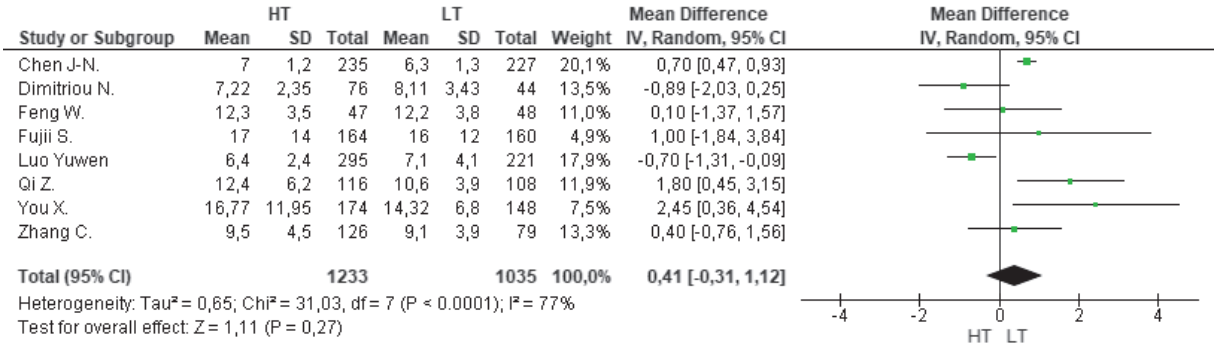

Figure 9. *Postoperative hospital stay*

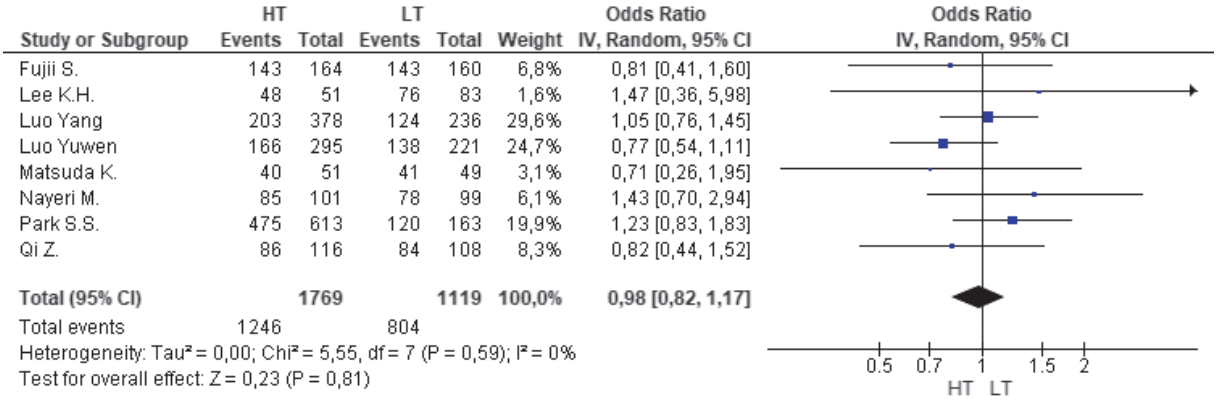

Figure 10. *5-year disease-free survival*

ligation with the preservation of LCA, the risk of colorectal anastomosis leakage is 1.6 times lower than in patients who underwent high IMA ligation (OR = 1.60; CI 1.23–2.10; p = 0.0006). Indeed, a significant factor is the blood supply of the rectum. So, Seike K. et al. made a study of blood flow through the marginal vessel using Laser Doppler in patients operated for rectosigmoid cancer. Authors have shown that blood flow in the rectum is better, and the rate of anastomosis leakage is lower in patients with preserved LCA [3]. However, the data of the presented sub-analysis comparing the rate of AL among randomized studies showed that there were no significant differences in the ligation of the IMA at the base and distal to the LCA (OR = 1.28; CI 0.82–2.00; p = 0.28).

It is important to emphasize that high IMA ligation correlates with damage to hypogastric nerves, and this, in turn, may contribute to an increase in the rate of genitourinary dysfunction [30, 31]. However, the study by Guraya S.Y. did not provide data on a significantly higher rate of urinary retention and sexual dysfunction [32]. This coincides with the results we have obtained: significant differences in the rate of urinary retention among patients with high and low IMA ligation were not revealed (OR = 1.23; CI 0.6–2.49; p = 0.57). In sub-analysis among randomized trials, the rate of urinary dysfunction also did not differ significantly in patients of both groups (OR = 1.43; CI 0.53–3.82; p = 0.48). In the treatment of rectal cancer and sigmoid cancer, it is important to take into account the possible damage to the apical lymph nodes. Thus, according to Yin, T-C.'s study, the apical lymph nodes were affected in 3.6% of cases [42]. There is an opinion [2] that high IMA ligation contributes to a more complete removal of apical lymph nodes, and thereby potentially

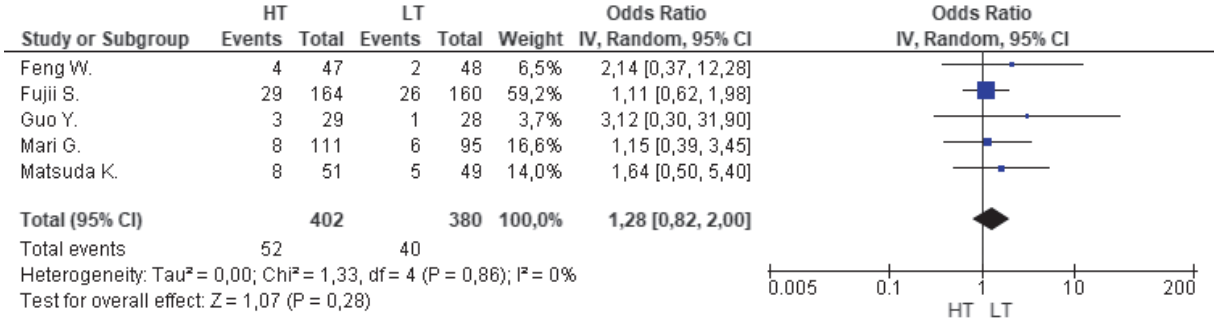

Figure 11. *Anastomotic leakage (according to randomized trials)*

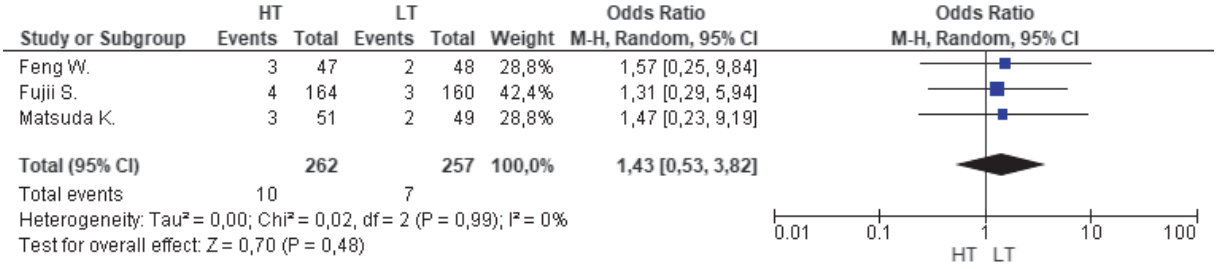

Figure 12. *Urinary dysfunction (according to randomized trials)*

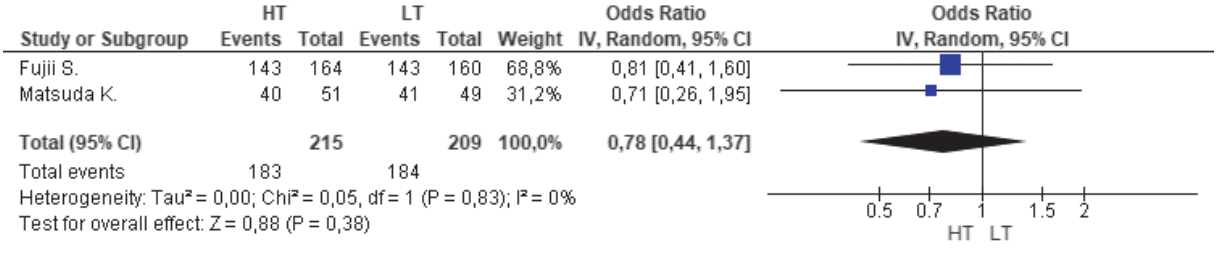

Figure 13. *5-year disease-free survival (according to randomized trials)*

improves the prognosis of the disease, while the staging of cancer is more accurate.

At the same time, a meta-analysis by Cirocchi R. showed that the method of IMA ligation does not affect the 5-year survival of patients (OR = 1.19; CI 0.889–1.58; $p = 0.24$) [33]. In this meta-analysis, there were no significant differences in the number of detected lymph nodes (the mean difference = 0.01; CI –0.82–0.83; $p = 0.99$). There were also no significant differences in the 5-year disease-free survival among patients, depending on the level of IMA ligation, in the analysis among all the studies included in the presented systematic review (OR = 0.98; CI 0.82–1.17; $p = 0.81$) as well as in the sub-analysis of randomized trials (OR = 0.78; CI 0.44–1.37; $p = 0.38$).

According to Hida J., high IMA ligation is technically faster and easier to do than ligation the IMA with the preservation of LCA [34]. On the contrary, Fan Y-C., et al., showed no significant differences in the time of the ligation stage of the procedure (the mean difference = 12.08; CI –0.86–25.01; $p = 0.07$) [35]. In the presented meta-analysis, there were also no significant differences in the operative time with high and low IMA ligation (the mean difference = –5.12; CI –11.22–0.97; $p = 0.10$).

The presented meta-analysis did not reveal significant differences between the groups in the incidence of mobilization of the left flexure (OR = 2.03; CI 0.69–5.98; $p = 0.20$). Seike K. noted that the preservation of the left colon artery provides more adequate blood flow in the anastomosis area [3]. Indeed, the preservation of LCA improves the rectum blood supply. However, on the technical side, LCA can be a limiting factor in the approximation and formation of a low anastomosis, even with a mobilized left flexure. So, Nano M. in one of his studies showed that routine mobilization of the left flexurewas required in the case of coloanal anastomosis or a colonic pouch, where a large length of the lowered intestine was really necessary [36].

Also, it should be noted, the peculiarities of the blood supply to the left flexure, when in 43% of cases there may be no anastomosis between the middle and left colic arteries — Griffiths point, and the blood supply to the left colon may be compromised [37].

There are two opposing opinions regarding the mobilization of the left flexure. Rondelli F. et al., basing on the meta-analysis which included 14 studies and 42,221 patients, provides data that routine mobilization of the left flexure is safe and does not increase the rate of postoperative complications, including the leakage of colorectal anastomosis (OR = 1.03; CI 0.92–1.15; $p = 0.59$), and also does not affect the late results [38]. At the same time, Chand M., et al., showed that the mobilization of the left flexure is a technically complicated and risky stage, and in cases where an anastomosis can be formed without tension of the sigmoid colon, it is not necessary to routinely perform the mobilization of the left flexure [39].

CONCLUSION

Thus, the results of the presented meta-analysis showed that the preservation of LCA is the main factor in improving the blood supply to the sigmoid colon and the rectum and statistically significantly reduces the incidence of colorectal anastomosis leakage in patients with rectal cancer.

AUTHORS CONTRIBUTION

Concept and design of the study: *Stanislav V. Chernyshov, Evgeny G. Rybakov*
Collection and processing of the material: *Mikhail A. Tarasov, Rashid I. Fayzulin*
Statistical processing: *Alexey A. Ponomarenko, Rashid I. Fayzulin*
Writing of the text: *Rashid I. Fayzulin*
Editing: *Evgeny G. Rybakov, Stanislav V. Chernyshov*

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