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Role of fluorescence navigation with indocyanine green during lateral pelvic lymphodissection in the treatment of rectal cancer (meta-analysis)

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ABSTRACT *INTRODUCTION: intraoperative fluorescence navigation with indocyanine green (ICG) allows visualizing possible affected lymph nodes, which hypothetically provides more precise lateral pelvic node dissection (LPND).*
AIM: to compare immediate results of lateral pelvic node dissection (LPND) combined with fluorescence navigation with ICG and conventional LPND for the treatment of metastatic lesions of lateral pelvic lymph nodes in patients with rectal cancer.
PATIENTS AND METHODS: search was performed in the PubMed library (National Library of Medicine, Bethesda, MD, USA) with keywords "indocyanine green," "ICG", "lymph nodes," "lateral lymph node dissection," and "rectal cancer" in various combinations. Four non-randomized studies were included in meta-analysis, three retrospective and one prospective, on the outcomes of ICG use during LPND in patients with rectal cancer in the meta-analysis.
RESULTS: significantly more lymph nodes were harvested in LPND + ICG group (MD = 4.5; 95% CI: 3.0–5.9; p < 0.00001). The operation time was longer in the ICG group (MD = 32.5; 95% CI: 2.8–62.3; p = 0.03). Intraoperative blood loss was higher in conventional LPND group (MD = –52.6; 95% CI: –89.8 — –15.3; p = 0.006). Hospital stay was significantly shorter in ICG group (MD = –1.2; 95% CI: –2.0 — –0.4; p = 0.003). Patients who underwent standard LPND were significantly more likely to have postoperative urinary retention (OR = 0.4; 95% CI: 0.1–0.9; p = 0.03).
CONCLUSION: fluorescence navigation with ICG improves early results of LPND. Further accumulation of experience with dynamic follow-up of patients is crucial.

KEYWORDS: *"indocyanine green," "ICG," "lymph nodes," "lateral lymph node dissection", "rectal cancer"*

CONFLICT OF INTEREST: *the authors declare no conflict of interest*

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INTRODUCTION

In Russia, rectal cancer ranks third in the incidence of malignant neoplasms of the digestive system and seventh in the overall structure of oncological morbidity [1].

In patients with cancer of the middle and low rectum, metastatically affected lateral pelvic lymph nodes (LPLN) are detected in 6–15% of cases [2]. The rate of local recurrence in patients with rectal cancer after surgery s 5.6% [3]. Metastases in lateral pelvic lymph nodes in patients with stage III of the disease dramatically worsens overall survival in comparison with the group of patients in whom these lymph nodes are not affected (45.8% vs. 71.2%, $p < 0.0001$) [4]. Bilateral lateral pelvic lymphodissection (LPLD), which is a routine treatment method in Japan and South Korea, is aimed at the preventive removal of all lymph nodes in the basin of the internal iliac vessels, which may be affected by metastases [5–7]. However, the oncological feasibility of routine pelvic lymph node

dissection is challenging. Thus, according to the results of a randomized study of Tsukamoto et al., the 7-year disease-free survival rate was 85.3% in the TME + LPLD group and 80.3% in the TME group with a risk ratio of 1.36 (from 0.98 to 1.90). However, the cumulative incidence of local recurrences was significantly lower in the TME + LPLD group (7.5% vs. 12.7%) with a risk ratio of 1.75 (from 1.09 to 2.82). At the same time, the only difference in the structure of local recurrences between the groups was a decrease in the rate of lateral recurrences in the TME + LPLD group [8]. One of the limitations of routine pelvic lymph node dissection is also an increased risk of postoperative morbidity such as bleeding, impaired urination, sexual dysfunction, small bowel obstruction, wound infection [9,10].

Intraoperative fluorescent navigation with indocyanin green (ICG) makes it possible to visualize possible affected lymph nodes with peritumoral submucosal injection of the agent, which hypothetically provides more precise lymph dissection and better postoperative results [11].

In order to compare the early results of LPLD in combination with fluorescent navigation with ICG and conventional LPLD for the treatment of metastatic lesions of the lateral pelvic lymph nodes in patients with rectal cancer, this meta-analysis was performed.

MATERIALS AND METHODS

The meta-analysis was performed in accordance with the recommendations (PRISMA). The search for scientific papers was conducted in the electronic database of medical literature PubMed (National Library of Medicine, Bethesda, MD, USA). Search keywords were as follows: “indocyanine green,” “ICG,” “lymph nodes,” “lateral lymph node dissection”, “rectal cancer” in various combinations. When searching for literature in a scientific electronic library elibrary.ru, no study was found on this topic. The meta-analysis includes full-text articles in English. When searching for literature in PubMed, 177 publications were found. After screening, 13 full-text articles were selected for this meta-analysis. In the future, literature reviews and interim results of randomized clinical trials are excluded. As a result of the literature selection, 4 non–randomized studies were included in the meta-analysis: three retrospective and one prospective, devoted to the results of ICG use during LPLD in patients with rectal cancer (Fig. 1). The main estimated indicators of the meta-analysis were: the number of removed lymph nodes, the surgery duration, blood loss, hospital stay and the number of urological morbidity (Table 1).

Statistical Analysis

The Review Manager 5.4.1 (The Cochrane Collaboration) program was used. The total value of the dichotomous data is described as an odds ratio (OR) with a coincidence interval (CI) equal to 95%. Continuous data are described by a non-standardized weighted average with 95% CI. Statistical heterogeneity among the included studies was assessed using the χ^2-test. Heterogeneity was assessed using I^2. Thus, at $I^2 < 50\%$, the heterogeneity was insignificant or moderate; on the contrary, at $I^2 > 50\%$, there was a high heterogeneity of studies, All the models

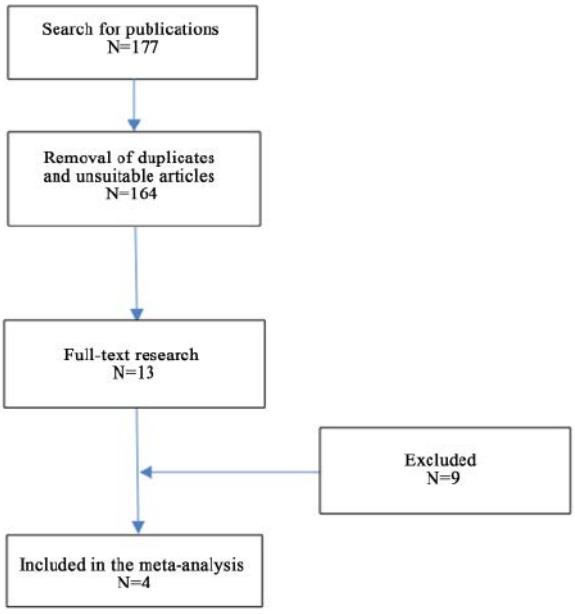

Figure 1. *Block diagram of literature search*

Table 1. *Characteristics of the included studies*

Author	Year	Country	Design	The number of patients	Surgeries	The number of removed lymph nodes	Surgery duration	Blood loss	Hospital stay (days)	Urological morbidity
Zhou et al. [12]	2019	China	Retrospective	42	LPLD with ICG — 12	11.5 ± 5.9	255.7 ± 65.2	55.8 ± 37.5	9.2 ± 1.6	0
					LPLD without ICG — 30	7.1 ± 4.8	273.1 ± 73.3	108.0 ± 52.7	9.7 ± 2.0	0
Dai et al. [13]	2022	China	Retrospective	40	LPLD with ICG — 20	19.2 ± 6.6	386 ± 45	22 ± 9	6 ± 2.2	0
					LPLD without ICG — 20	15 ± 4.6	332 ± 48	89 ± 14	8 ± 3.4	2
Tang et al. [14]	2023	China	Prospective	79	LPLD with ICG — 29	12 (8–19)	275 (230–333)	30 (30–100)	5 (5–6)	0
					LPLD without ICG — 50	9 (6–13)	256 (210–300)	30 (20–50)	6 (5–8)	8
Watanabe et al. [15]	2023	Japan	Retrospective	116	LPLD with ICG — 58	14 (10–18)	426 (382–457)	13 (5–125)	14 (10–19)	7
					LPLD without ICG — 58	9 (5–11)	369 (324–411)	110 (35–188)	17 (13–21)	13

were presented with a random effect. The differences were considered statistically significant at $p < 0.05$.

RESULTS

The meta-analysis included 277 patients with rectal cancer, of whom 119 patients underwent lateral pelvic lymph node dissection with fluorescent ICG navigation, and 158 patients underwent standard LPLD (Table 1).

LPLD in combination with fluorescent navigation with ICG, compared with conventional lateral pelvic lymph node dissection, more lymph nodes are significantly removed (The difference average = 4.5; 95% CI: 3.0–5.9; $p < 0.00001$), which

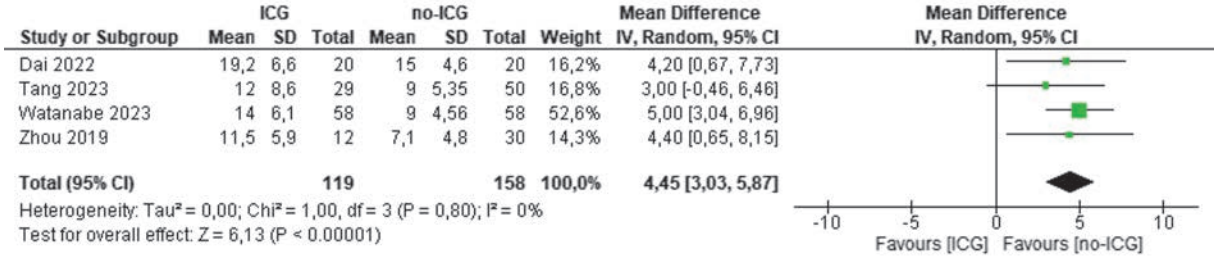

Figure 2. *Number of harvested lateral pelvic lymph nodes*

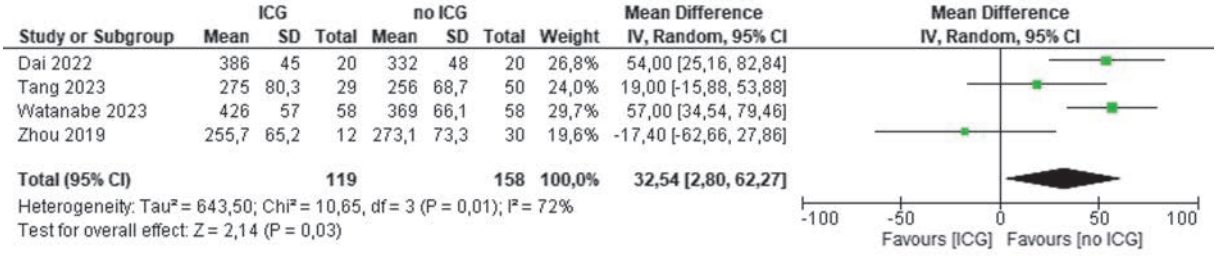

Figure 3. *Operative time*

is confirmed by the absence of heterogeneity (I2 = 0%) (Fig. 2).

The operation time with indocyanine green is significantly longer than standard LPLD (Mean difference = 32.5; 95% CI: 2.8–62.3; p = 0.03).However, the high heterogeneity of the studies does not allow for unambiguous interpretation of the data obtained (I^2 = 72%) (Fig. 3).

Similarly, there is a significant difference (Mean difference = –52.6; 95% CI: –89.8 — –15.3; p = 0.006) in intraoperative blood loss with a shift for the worse in patients with conventional lateral pelvic lymph node dissection. Nevertheless, according to this, there is also an extremely high heterogeneity of studies (I^2 = 92%) (Fig. 4).

Hospital stay was significantly shorter in patients who underwent LPLD in combination with fluorescent navigation with ICG (Mean difference = –1.2; 95% CI: –2.0 — –0.4; p = 0.003, I^2 = 35%) (Fig. 5).

Similarly, it can be said with a high degree of confidence that patients who underwent standard LPLD are much more likely to postoperative urinary retention (23 out of 158; 15%) than in the group with fluorescent navigation with ICG (7 out of 119; 6%) (OR = 0.4; 95% CI: 0.2–0.9; p = 0.03) (I^2 = 0%) (Fig. 6).

DISCUSSION

There are two approaches to lateral pelvic lymph node dissection — preventive and curative. The first principle is widespread in eastern countries, and therefore TME with LPLD is performed routinely in middle-lower ampullary rectal cancer [13]. In

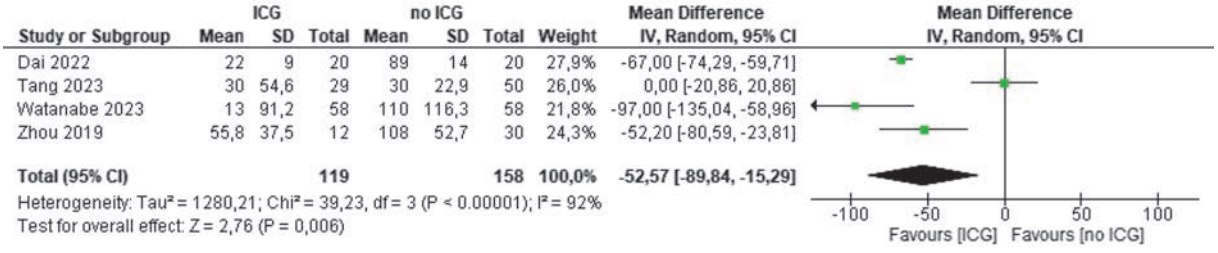

Figure 4. *Bloodloss*

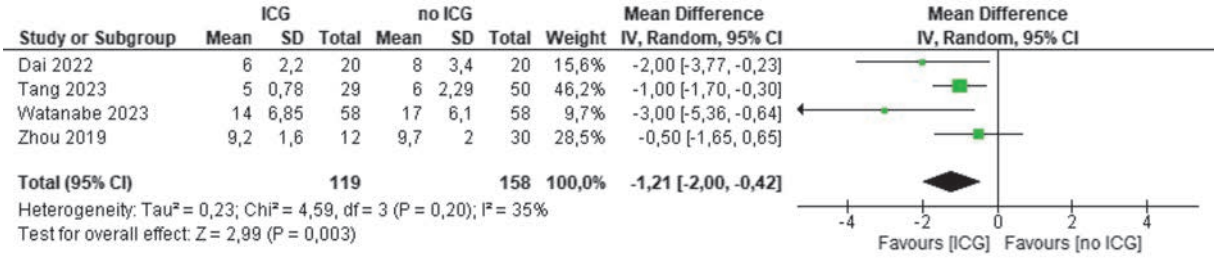

Figure 5. *Hospital stay*

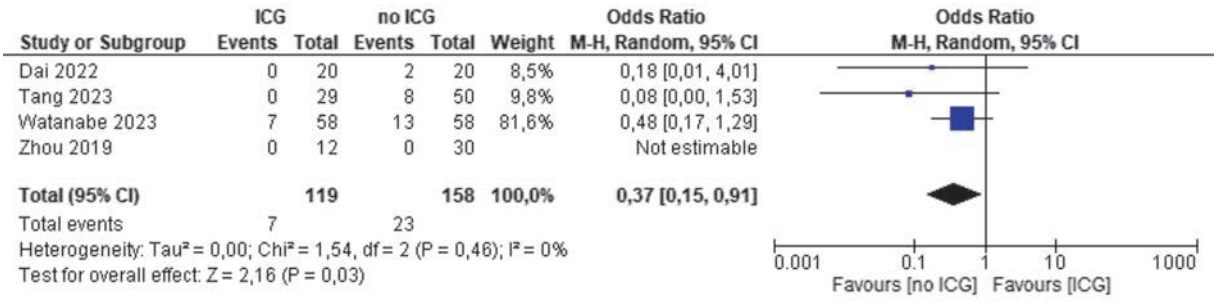

Figure 6. *Urinary retention*

Western countries, LPLD is performed only if the presence of metastatically affected lymph nodes is suspected. The studies included in this meta-analysis appealed to preventive pelvic lymph node dissection.

A comparative analysis of the results of 4 trials for comparison of lateral pelvic lymph node dissection in combination with fluorescent navigation with ICG and standard LPLD was carried out. It showed the advantages of the method in terms of increasing the number of lymph nodes to be removed (Mean difference = 4.5; 95% CI: 3.0–5.9; $p < 0.00001$), reducing blood loss (Mean difference = –52.6; 95% CI: –89.8 — –15.3; $p = 0.006$), hospital stay (Mean difference = –1.21; 95% CI: –2.00 — –0.42; $p = 0.003$) and the number of urological morbidity (OR = 0.4; 95% CI: 0.2–0.9; $p = 0.03$).

The use of indocyanine green provides better visualization of the affected lymph nodes, more accurate differentiation of surrounding tissues, and, accordingly, a lower probability of damage to nearby blood vessels, a lower level of blood loss and postoperative morbidity associated with injury of adjacent structures. Also, the low rate of intraoperative bloodloss may correlate with more precise surgery.

However, it is worth noting that ICG accumulates both in intact lymph nodes and in metastatically affected ones, which does not allow for the identification of affected lymph nodes with high accuracy [12,16].

The analysis of the results also revealed an increase in the operation time by about 32 minutes in the LPLD group with fluorescent navigation with ICG (Mean difference = 32.5; 95%; CI: 2.8–62.3; $p = 0.03$). Given that the procedure of peritumoral submucosal injection of the agent takes a short time, the resulting time difference can be attributed to a small number of patients and the lack of elaboration of the technique. It is worth noting that according to our meta-analysis, more lymph nodes are removed during fluorescent navigation, which may also cause a difference in the operation time.

A larger lymph nodes harvest during fluorescent navigation can also potentially affect oncological results.

Nevertheless, data on this issue are currently limited, Zhou and Dai in their studies note the absence of local recurrence in patients who underwent LPLD in combination with fluorescent navigation with ICG [12,13]. However, the study of Watanabe J., with the currently largest number of patients included and the time of follow-up, did not show a significant difference in the rate of local recurrences in the ICG group compared with standard LPLD ($p = 0.542$) [15].

This meta-analysis has a number of significant limitations, and therefore its results should be interpreted carefully. First of all, it is the non-randomized and retrospective studies, as well as the small cohorts, which could lead to a risk of bias. Additional limitations are imposed by high heterogeneity in most indicators. The absence or insufficiency of primary data, especially in early results, could also distort the trial and did not allow for a full-fledged analysis of other characteristics. Similarly, it is currently not possible to analyze the late results. Thus, it is quite difficult to draw unambiguous conclusions due to the small number of carefully planned studies on this problem. Further accumulation of experience with follow-up is necessary to assess immediate and long-term results.

CONCLUSION

The addition of fluorescent navigation with ICG improves standard LPLD in terms of increasing the number of removed lymph nodes (Mean difference = 4.5; 95% CI: 3.0–5.9), reducing intraoperative blood loss (Mean difference = –52.6; 95% CI: –89.8 — –15.3) and hospital stay (Mean difference = –1.2; 95% DI: –2.0 — –0.4). There is also a decrease in the rate of postoperative acute urinary retention (OR = 0.4; 95% CI: 0.1–0.9).

AUTHORS CONTRIBUTION

Concept and design of the study: *Ilya S. Tishkevich, Mikhail V. Alekseev*

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