# FLUORESCENCE-GUIDED LYMPHATIC MAPPING IN PATIENTS WITH DIFFERENTIATED THYROID CANCER

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## Abstract

The role of prophylactic central neck dissection in patients with differentiated thyroid cancer without clinically evident lymph node involvement remains controversial despite its importance for staging and risk stratification. In this context, intraoperative lymphatic mapping may provide an opportunity to reduce the extent of surgical intervention.

The study included 125 patients with cN0 differentiated thyroid cancer who underwent thyroidectomy or hemityroidectomy. Central neck dissection was performed in 98 patients, while 27 patients underwent fluorescence-guided lymphatic mapping using indocyanine green with selective lymph node removal. The mean number of removed lymph nodes was significantly lower in the ICG group (3.67 vs 10.3; $p < 0.001$), while the rate of metastatic node detection did not differ between groups (33.3% vs 34.7%; $p = 0.62$). The incidence of transient hypoparathyroidism was comparable (14.8% vs 13.3%; $p = 0.74$), whereas permanent hypoparathyroidism was observed only in the central neck dissection group (17.3% vs 0%; $p = 0.02$). However, in the subgroup of patients undergoing thyroidectomy, no difference in transient hypoparathyroidism was found (15.5% vs 15.4%; $p = 1.00$). Permanent recurrent laryngeal nerve palsy occurred in 4.1% of patients in the control group and was not observed in the ICG group.

These findings suggest that fluorescence-guided lymphatic mapping allows selective lymph node removal with a reduced extent of dissection while maintaining a comparable rate of metastatic detection. The differences in postoperative complications appear to be primarily related to the extent of surgery. Further studies are required to evaluate the diagnostic accuracy and long-term outcomes of this approach.

**Key words:** indocyanine green, fluorescence imaging, lymphatic mapping, differentiated thyroid cancer, lymph node dissection, thyroidectomy

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# ПРИМЕНЕНИЕ ФЛУОРЕСЦЕНТНОГО КАРТИРОВАНИЯ ЛИМФООТТОКА У ПАЦИЕНТОВ С ДИФФЕРЕНЦИРОВАННЫМ РАКОМ ЩИТОВИДНОЙ ЖЕЛЕЗЫ

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## Резюме

Целесообразность профилактической центральной лимфаденэктомии у пациентов с дифференцированным раком щитовидной железы (ЩЖ) без клинических признаков поражения лимфатических узлов остаётся предметом дискуссии, несмотря на её значение для уточнения стадии заболевания и стратификации риска рецидива. В связи с этим представляют интерес методы интраоперационного картирования лимфатического оттока, позволяющие ограничить объём хирургического вмешательства.

В исследование включено 125 пациентов с cN0 дифференцированным раком ЩЖ, которым была проведена тиреоидэктомия либо гемитиреоидэктомия. У 98 пациентов выполнена центральная лимфаденэктомия, у 27 – флуоресцентное картирование лимфатического оттока с использованием индоцианина зелёного (ИЦЗ) с последующим селективным удалением лимфатических узлов. Среднее

число удалённых лимфатических узлов было ниже в группе ИЦ3 (3,67 против 10,3; $p < 0,001$), при этом частота выявления метастатического поражения статистически не различалась (33,3% и 34,7%; $p = 0,62$). Частота транзиторного гипопаратиреоза была сопоставимой между группами (14,8% и 13,3%; $p = 0,74$), тогда как постоянный гипопаратиреоз отмечен только в группе центральной лимфаденэктомии (17,3% против 0%; $p = 0,02$). При анализе пациентов, перенесших тиреоидэктомию, различия в частоте транзиторного гипопаратиреоза отсутствовали (15,5% и 15,4%; $p = 1,00$). Постоянный парез возвратного гортанного нерва отмечен у 4,1% пациентов в группе ЦЛД и не наблюдался в группе ИЦ3.
Полученные данные свидетельствуют о возможности выполнения селективного удаления лимфатических узлов на основании результатов флуоресцентного картирования для стадирования заболевания и определения послеоперационного лечения больных. Различия в частоте осложнений, вероятно, связаны с объёмом хирургического вмешательства. Для оценки диагностической точности метода и его влияния на отдалённые результаты необходимы дальнейшие исследования.

**Ключевые слова:** дифференцированный рак щитовидной железы, индоцианин зелёный, флуоресцентная визуализация, лимфатическое картирование, лимфодиссекция, тиреоидэктомия.

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## Introduction

Differentiated thyroid cancer (DTC), which includes papillary thyroid carcinoma (PTC), follicular carcinoma, and oncocytic carcinoma, accounts for more than 90% of all malignant neoplasms of the thyroid gland (TG) and represents the most common form of endocrine cancer [1]. In recent decades, a steady increase in the incidence of DTC has been observed in many countries worldwide [2,3]. According to GLOBOCAN 2020, more than 580,000 new cases of thyroid cancer are registered annually worldwide [2]. In the Russian Federation, approximately 12,000 new patients are registered annually [4]. Despite a high 10-year survival rate exceeding 90%, disease recurrence can be detected in a significant proportion of patients and is generally dependent on the number of affected lymph nodes in the central compartment [3,5]. According to surgical and pathomorphological studies, involvement of regional lymph nodes is detected in 30–80% of patients with DTC in the absence of clinical signs of their involvement, with the frequency substantially depending on the extent of lymph node dissection and the thoroughness of morphological analysis [6,7]. The central compartment (paratracheal lymph nodes or level VI) is the most common site of primary metastasis [6].

Given the high frequency of lymphogenous metastasis, the need for prophylactic central lymph node dissection in the absence of clinical signs of regional lymph node involvement (cN0) has been widely discussed in recent years. On the one hand, prophylactic central lymphadenectomy allows for accurate disease staging. At the same time, a number of studies have shown that performing prophylactic central lymph node dissection does not lead to a significant improvement in long-term treatment outcomes [8]. Prophylactic central lymph node dissection is falling out of routine practice, as its performance may be accompanied by an increased risk of postoperative complications, primarily hypoparathyroidism and recurrent laryngeal nerve (RLN) injury [9].

In current guidelines for the management of patients with DTC, a key role is given to stratifying the risk of disease recurrence. According to the American Thyroid Association (ATA, 2025) guidelines, the assessment of local recurrence risk is based on a combination of clinical and morphological factors, including the size and location of the primary tumor, the presence of extrathyroidal extension, histological features of the tumor, and the status of regional lymph nodes [1]. Based on these data, patients are stratified into low-risk, low-intermediate risk, intermediate-high risk, and high-risk of recurrence groups, thereby determining postoperative treatment or observation strategies. One of the main criteria for risk stratification is histologically confirmed lymph node involvement.

Routine abandonment of central lymphadenectomy may lead to underestimation of regional metastasis status and incorrect choice of postoperative management strategy. In turn, this may lead to an increased rate of recurrence or disease progression. Of particular interest is the use of lymphatic drainage mapping techniques. Identifying lymph nodes involved in the lymphatic drainage from the tumor could potentially contribute to a more accurate assessment of the regional extent of the tumor process without increasing the rate of postoperative complications.

One of the current directions in the development of intraoperative navigation is the use of fluorescence diagnostics with indocyanine green (ICG). After injection of the dye into the thyroid tissue, it binds to proteins in the interstitial fluid and plasma and spreads through the lymphatic vessels, allowing visualization of lymphatic drainage using a near-infrared fluorescence imaging system.

Aim of the study is to develop and investigate the necessity of a method for intraoperative fluorescence mapping of lymphatic drainage in differentiated thyroid cancer.

## Materials and Methods

An open prospective study with a retrospective control group was conducted at the N.N. Burdenko Clinic of Faculty Surgery.

For intraoperative mapping of lymphatic pathways, 0.1 ml of ICG (0.5 mg/ml; Fig. 1) was injected into the thyroid tumor under ultrasound guidance 15 minutes before the skin incision. After completion of the main stage of the operation – thyroidectomy or hemithyroidectomy – the regional drainage zones were identified using a Stryker SPY-PHI near-infrared fluorescence imaging system (Fig. 2). The intraoperative photograph shows fluorescence of lymphatic vessels and regional lymph nodes (marked with a square) in the near-infrared range. The collector or tissue containing lymph nodes draining the injection zone was identified. The identified area of tissue with lymph nodes was excised. The removed thyroid gland or thyroid lobe with the selectively excised tissue was sent for routine histological examination. Based on the results of the routine histological examination, the postoperative clinical diagnosis was formulated, the disease stage was determined, the further treatment plan was established, and the follow-up program was defined.

***Inclusion criteria for patients in the study:***

1. Newly diagnosed DTC: category VI or V according to the results of a cytological examination of the punctate nodule according to the Bethesda System with a normal level of calcitonin in the blood.
2. Stages T1-T3 according to the TNM classification 9th edition.
3. Absence of clinical signs of metastasis – cN0, cM0.
4. Planned surgical treatment – thyroidectomy or hemithyroidectomy.

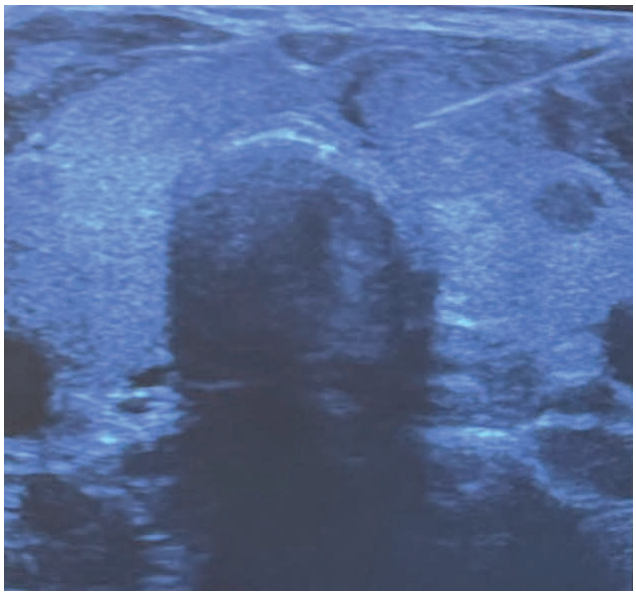

**Рис. 1.** Ультразвуковая сканограмма. Введение ИЦЗ в опухоль ЩЖ под контролем УЗИ.
**Fig. 1.** Ultrasound scan. Intratumoral ultrasound-guided injection of ICG.

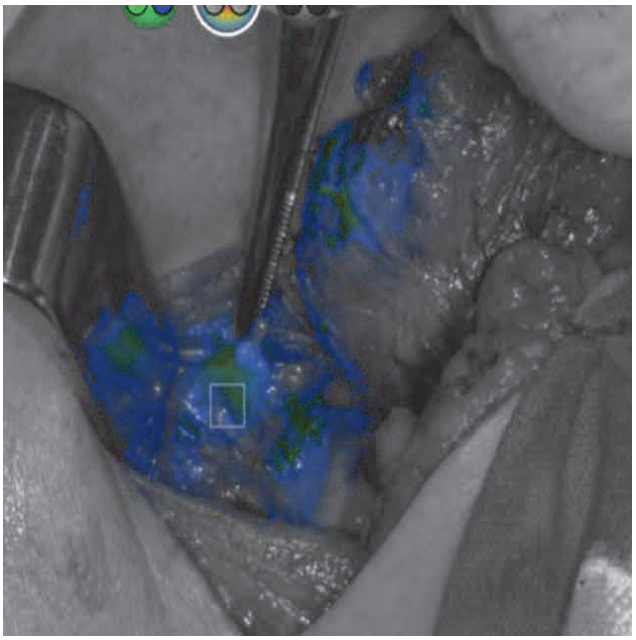

**Рис. 2.** Пути лимфатического оттока после введения ИЦЗ.
**Fig. 2.** The pathways of lymphatic outflow after the introduction of ICG.

5. Patient age from 18 to 75 years.
6. Signed informed consent to participate in the study.

***Non-inclusion criteria:***

1. Recurrent forms of thyroid cancer.
2. Presence of regional and distant metastases – N+ and/or M+.
3. Allergic reactions to ICG in history.
4. Pregnancy and lactation period.
5. Severe concomitant diseases: chronic heart failure class III-IV, renal failure.

***Exclusion criteria:***

1. Absence of signs of a malignant process according to the results of postoperative histological examination.
2. Cancer type confirmed by postoperative histological examination that is not DTC.
3. Patient's refusal to continue participation in the study.

## Results

The study included 125 patients operated on at the Clinic of Faculty Surgery from 2023 to 2025. In 98 cases, thyroidectomy or hemithyroidectomy was performed with central lymph node dissection (CLND), and in 27 cases, thyroidectomy or hemithyroidectomy was supplemented with intraoperative lymphatic drainage mapping using ICG followed by selective excision of lymph nodes (Table 1). The mean age of patients in the CLND group was 47 (39-59) years, and in the ICG group – 43 (33-45) years ($p = 0.12$). In the CLND group, the proportion of men was 17.3%, in the ICG group – 33.3%, no statistically significant differences in sex were found between the groups ($p = 0.29$).

Thyroidectomy was performed in 71 (72.4%) patients in the CLND group and in 13 (48.1%) patients in the ICG group (p = 0.08). The mean number of removed lymph nodes in the control group was 10.3 per patient, whereas in the ICG group it was 3.67 (Mann-Whitney U test, ***p <0.001). Metastatic lymph node involvement according to histological examination was detected in 34 (34.7%) patients in the CLND group and in 9 (33.3%) patients in the ICG group (p = 0.62).

Transient hypoparathyroidism was registered in 13 (13.3%) patients in the control group and in 4 (14.8%) patients in the ICG group; the differences did not reach statistical significance (p = 0.74). Permanent hypoparathyroidism developed in 17 (17.3%) patients in the control group and was not registered in the ICG group (p = 0.02). Transient recurrent laryngeal nerve palsy was detected in 16 (16.3%) patients in the control group and in 2 (7.4%) patients in the ICG group (p = 0.32). Permanent recurrent laryngeal nerve palsy was not registered in the ICG group.

When analyzing the subgroup of patients who underwent thyroidectomy, transient hypoparathyroidism was registered in 11 (15.5%) out of 71 patients in the CLND group and in 2 (15.4%) out of 13 patients in the ICG group; no statistically significant differences were found between the groups (p = 1.00). Permanent hypoparathyroidism developed in 17 (23.9%) out of 71 patients in the control group, whereas no such complication occurred in the ICG group; the differences did not reach statistical significance (p = 0.061; Table 2). Permanent RLN palsy developed in 4 (4.1%) patients in the control group and was not registered in the ICG group (p = 0.57).

## Discussion

Intraoperative fluorescence mapping of lymphatic drainage may potentially be used for disease staging in settings where prophylactic lymphadenectomy is not indicated. At the same time, the rate of detecting metastatic lymph node involvement did not differ statistically between the groups. The comparable rate of metastasis detection with a significant reduction in the number of removed lymph nodes may indicate the possibility of targeted removal of nodes specifically involved in lymphatic drainage from the tumor. A similar principle underlies sentinel lymph node biopsy. The possibility of its application in PTC has been discussed previously, including studies on the use of ICG for intraoperative lymphatic mapping [9,10].

Although performing central lymph node dissection increases the accuracy of staging and is used for recurrence risk stratification [1], meta-analysis data do not confirm its impact on long-term oncological outcomes. At the same time, an increased rate of postoperative complications has been noted [8,11], particularly hypoparathyroidism and RLN palsy. With a comparable rate of postoperative

**Таблица 1**
**Характеристика пациентов**
**Table 1**
**Baseline characteristics**

| Показатель Variable | Число наблюдений, абс. (%) Number of observations, abs. (%) | | p-value |
|---|---|---|---|
| | ЦЛД CLND | ИЦЗ ICG | |
| Всего In total | 98 | 27 | - |
| Мужчин Men | 17 (17,3) | 9 (33,3) | 0,29 |
| Перенесших тиреоидэктомию Thyroidectomy | 71 (72,4) | 13 (48,1) | 0,08 |
| С опухолью T1 T1 tumor | 67 (68,4) | 21 (77,8) | 0,29 |
| С опухолью T2 T2 tumor | 12 (12,2) | 4 (14,8) | |
| С опухолью T3 T3 tumor | 19 (19,4) | 2 (7,4) | |

**Таблица 2**
**Хирургические результаты и послеоперационные осложнения**
**Table 2**
**Surgical outcomes and postoperative complications**

| Показатель Variable | Число наблюдений, абс. (%) Number of observations, abs. (%) | | p-value |
|---|---|---|---|
| | ЦЛД CLND | ИЦЗ ICG | |
| Всего In total | 98 | 27 | - |
| Метастазы в лимфоузлах Lymph node metastases | 34 (34,7) | 9 (33,3) | 0,62 |
| Транзиторный гипопаратиреоз Transient hypoparathyroidism | 13 (13,3) | 4 (14,8) | 0,74 |
| Пациентов с постоянным гипопаратиреозом Persistent hypoparathyroidism | 17 (17,3) | - | 0,02* |
| Транзиторный парез ВГН Transient paresis RLN | 16 (16,3) | 2 (7,4) | 0,32 |
| Постоянный парез ВГН Persistent RLN paresis | 4 (4,1) | - | 0,57 |

*результат статистически значим / the result is statistically significant

transient hypoparathyroidism, the rate of permanent hypoparathyroidism and the rate of postoperative RLN palsy were significantly lower in patients who underwent selective lymphadenectomy.

The use of ICG for intraoperative diagnostics is based on detecting a signal in the near-infrared range, which allows assessment of lymphatic drainage in real time. The method does not require ionizing radiation and can be integrated into the standard surgical protocol. At the same time, its application is limited by the depth of signal penetration and depends on the injection technique and visualization conditions [12,13]. A significant technical limitation of the method is the anatomically close location of the injection site to the potential area of sentinel lymph nodes. If the drug is injected incorrectly or if the thyroid tissue is inadvertently damaged during surgery, the drug may spread throughout the surgical field, making further lymphatic system mapping impossible.

The obtained data allow considering fluorescence mapping of lymphatic drainage using ICG as a potential and accessible tool for disease staging in patients with DTC without significantly increasing the extent of surgical intervention.

## Conclusion

Intraoperative fluorescence mapping of lymphatic drainage using ICG represents a reproducible and technologically accessible method that expands the possibilities of intraoperative navigation in differentiated thyroid cancer. The use of this method allows surgeons to rely on individual lymphatic drainage characteristics and perform selective removal of lymph nodes involved in drainage from the tumor.

Thus, more accurate determination of the disease stage is quite feasible using modern fluorescence mapping methods without increasing the complication rate. The identified differences in complication rates are likely primarily related to the extent of surgical intervention. Further studies are required for the final assessment of the clinical significance of the method.

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