Near-infrared fluorescence lymph node template region dissection plus backup lymphadenectomy in open radical cystectomy for bladder cancer using an innovative handheld device: a single center experience

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RESEARCH ARTICLE

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Near-infrared fluorescence lymph node template region dissection plus backup lymphadenectomy in open radical cystectomy for bladder cancer using an innovative handheld device: A single center experience

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Abstract

Background: The extent of pelvic lymphadenectomy (PLND) as part of radical cystectomy (RC) for bladder cancer (BC) remains unclear. Sentinel-based and lymphangiographic approaches could lead to reduced morbidity without sacrificing oncologic safety.

Objective: To evaluate the feasibility and diagnostic value of fluorescence-guided template sentinel region dissection (FTD) using a handheld near-infrared fluorescence (NIRF) camera in open radical cystectomy.

Design, Setting, and Participants: After peritumoral cystoscopic injection of indocyanine green (ICG) 21 patients underwent open RC with FTD due to BC between June 2019 and June 2021. Intraoperatively, the FIS-00 Hamamatsu Photonics® NIRF camera was used to identify and resect fluorescent template sentinel regions (FTRs) followed by extended pelvic lymphadenectomy (ePLND) as oncological back-up.

Outcome Measurement and Statistical Analysis: Descriptive analysis of positive and negative results per template region.

Results and Limitations: FTRs were identified in all 21 cases. Median time (range) from ICG injection to fluorescence detection was 75 (55–125) minutes. On average (SD), 33.4 (9.6) lymph nodes were dissected per patient. Considering template regions as the basis of analysis, 67 (38.3%) of 175 resected regions were NIRF-positive, with 13 (7.4%) regions harboring lymph node metastases. We found no metastatic lymph nodes in NIRF-negative template regions. Outside the standard template, two NIRF-positive benign nodes were identified.

Conclusion: The concept of NIRF-guided FTD proved for this group all lymph node metastases to be found in NIRF-positive template regions. Pending validation in a larger collective, resection of approximately 40% of standard regions may be sufficient and may result in less morbidity.

KEYWORDS
bladder cancer, near-infrared, NIRF, sentinel node

1 | INTRODUCTION

Bladder cancer (BC) represents the 10th most diagnosed cancer. The worldwide age-standardized incidence rate (per 100 000 person-years) is 9.5 in men and 2.4 in women.[1]

The standard treatment for muscle-invasive bladder cancer (MIBC) and well-selected patients with high-risk noninvasive BC is radical cystectomy with bilateral extended pelvic lymph node dissection (ePLND).[2] ePLND represents an integral part of radical cystectomy in MIBC as it defines adjuvant treatment needs and serves as a diagnostic tool to assess patient's prognosis.[3] It is unclear whether the extension of the standard PLND template leads to a prognostic improvement,[4,5] especially when neoadjuvant chemotherapy was performed. The LEA trial, indicated a 3%–8% occurrence of PLND-related complications such as lymphocele and lymphedema.[6] Because considerable crossover of lymphatic drainage occurs even in patients with entirely lateralized bladder tumors, bilateral lymph node dissection is generally preferred to unilateral lymphadenectomy.[7]

In an attempt to identify the first tumor-draining lymph nodes, and thereby the initial landing site of metastatic cancer cells, the sentinel lymph node (SLN) procedure has been introduced as diagnostic surgical procedure in various cancer types.[8–12] The histopathological examination of SLN's helps to optimize the precision of lymph node staging, without the a priori need for PLND. The SLN procedure has also been investigated and applied in various urological cancers, namely testis, prostate, bladder, and is an integral part of standard surgical therapy in penile cancer.[13–15] The feasibility and diagnostic value of SLN procedure in BC have been investigated using radio-guided methods with technetium radiocolloid, other using ICG fluorescence and one using the combination of the two.[16–24] Radio-guided methods of sentinel biopsy have certain drawbacks, such as the lack of visualization of the topographic localization of the tracer in the tissue and the organizational effort including radiation protection. Therefore, first promising experiences have been made with the use of intraoperative near-infrared fluorescence (NIRF) technique for sentinel node biopsy in BC.[19,20,22] As lymphangiographic ICG-guided procedures tend to identify more nodes than SLN-targeted procedures,[20] we propose ICG-guided template sentinel region dissection. In contrast to traditional SLN procedures, we believe that highlighting template sentinel regions could lead to a reduction in the extent of lymphadenectomy during radical cystectomy. As the feasibility of fluorescent and radio-guided SLN procedures was already shown in several studies but detection rates in these studies varied (23%–94%; 63% when combining both methods) our aim was to challenge whether template-based approaches could be performed without loss of oncological safety. Therefore, we chose an approach combining fluorescence-guided template sentinel region dissection (FTD) with ePLND as diagnostic and oncological backup to investigate the concept of an "individualized" lymphadenectomy in the future.

2 | MATERIALS AND METHOD

Between June 2019 and June 2021, 21 patients undergoing open radical cystectomy with FTD and ePLND due to MIBC or high-risk NMIBC were prospectively enrolled in this analysis. The study was approved by the local ethics committee (21-9935-BO) and conducted in accordance with the ethical standards of the Declaration of Helsinki. Diagnosis of BC was based on pathological examination after transurethral resection of the bladder tumor (TURBT) in patients older than 18 years. All patients gave written informed consent for radical cystectomy with fluorescent-guided lymphadenectomy before study inclusion. Inclusion criteria were presence of muscle-invasive urothelial carcinoma in adult (>18 years) patients eligible for radical cystectomy with alternative urinary diversion. Exclusion criteria were allergy to ICG, bronchial hyperreactivity, endocrine thyroid dysfunction, pregnancy, and lactation.

Surgical procedures: After induction of anesthesia, rigid cystoscopy was performed. ICG was dissolved with water and injected in a 5 mg/mL solution. A total of 2 mL was injected peritumorally in four fractions under cystoscopic control (Wolf® Cystoscope 12° 8.0'9.8 CH. NL:150MM GL:283MM) using a Williams Cystoscopy Injection Needle (5 FR 35 cm/8 mm, Cook Medical®). Afterward, radical cystectomy was performed via a median laparotomy and lymphadenectomy was performed using a CE-marked prototype handheld Fluorescent Imaging System-FIS-00 (Hamamatsu Photonics K.K.) for fluorescent imaging. Sterile draped Hamamatsu Photonics® camera (Figure 1) was used to identify sentinel regions (Figures 2 and 3). Accessible areas outside the standardized template were examined as well. The retroperitoneum is widely explored by default so that the aortic bifurcation can be inspected up to the junction of the inferior mesenteric artery. We used a lymphadenectomy template (Figure 2) according to the SAKK 6/17 study (NCT03406650). First, fluorescent template regions and fluorescent nodes outside the standard template were dissected followed by bilateral extended pelvic back-up lymphadenectomy (ePLND). The individual resected template regions were then placed on a prepared sheet indicating the ePLND template and subjected to a second confirmatory fluorescent examination (Figure 4). In all 21 cases, the procedures were performed by three experienced surgeons (Boris A. Hadaschik, Stephan Tschirdewahn, and

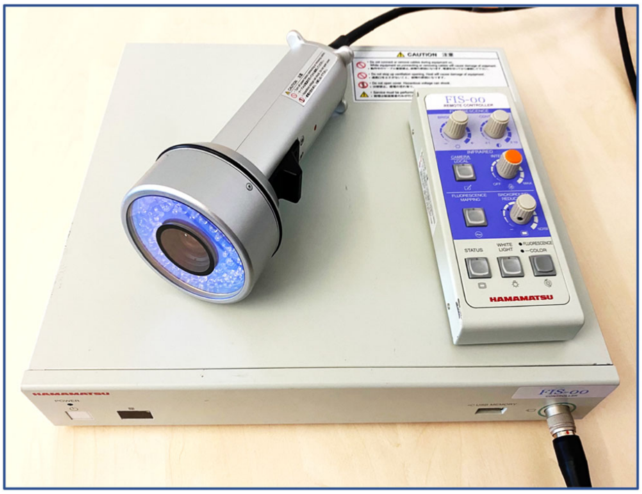

FIGURE 1 FIS-00, CE-marked prototype near-infrared fluorescence imager, Hamamatsu Photonics®.

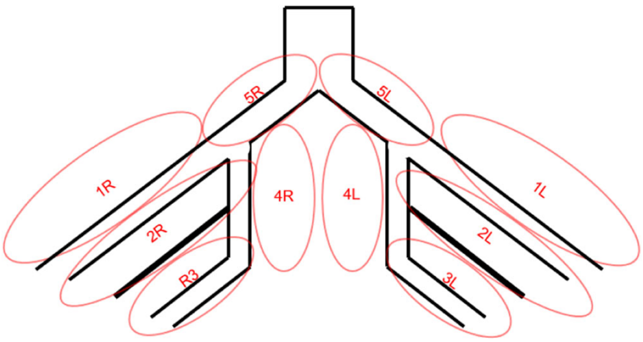

FIGURE 2 Lymphadenectomy template with visualization of sentinel template regions. R: right, L: left, 1R/1L: External iliac, 2R/2L: Obturator fossa, 3R/3L: Internal iliac, 4R/4L: Presacral, 5R/5L: Common iliac and aortic bifurcation.

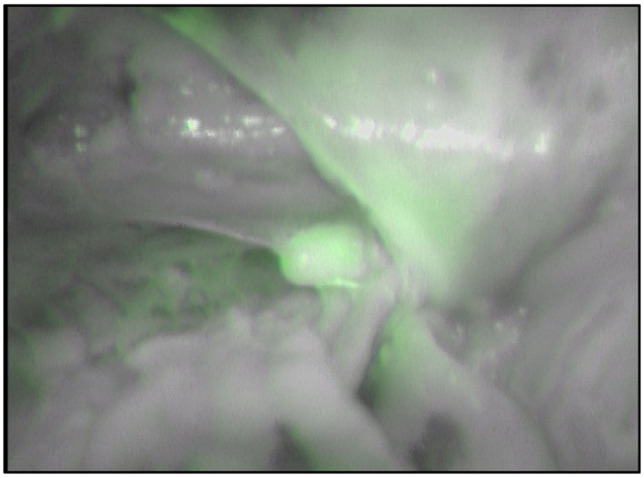

FIGURE 3 Intraoperative in vivo detection of a sentinel node (Cloquet).

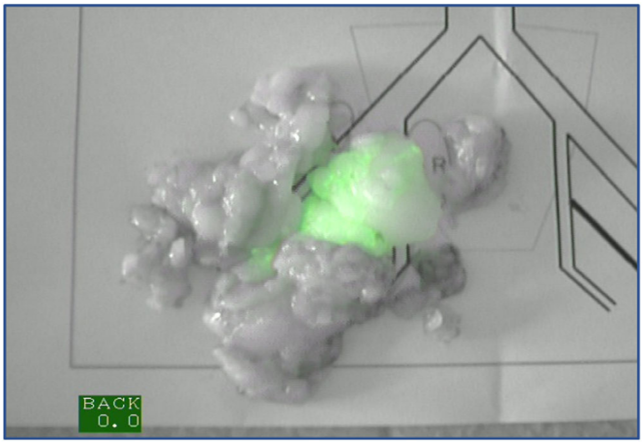

FIGURE 4 Example of a near-infrared fluorescence (NIRF)-positive area in template region 2R.

Jochen Hess), and histopathological specimens were examined by a dedicated uropathologist. All dissected lymph nodes were pathologically processed and examined in a standard manner.

We decided to use the term "false negative" to discuss results. We are very aware that a sentinel method is not a diagnostic test for the detection of lymph node metastases.

3 | RESULTS

A total of 21 patients underwent radical cystectomy with FTD and subsequent ePLND. Fluorescent regions could be identified in all cases, corresponding to an ICG-detectionof 100%. Three patients had previously received neoadjuvant platinum-based chemotherapy (NAC) and one patient had received NAC plus immunotherapy. The median age was 63 (33–78) years. The results of the pathological examination of the bladder and lymph node tissue are given in Table 1a and histopathological findings are shown in Table 1b. The urinary diversions chosen were ileal conduit, ileocecal pouch, and orthotopic neobladder in 16, 1, and 4 cases, respectively. The median time (range) from ICG injection to sentinel detection was 75 (55–125) minutes. Cystoscopic injection including repositioning and intraoperative detection of the sentinel regions increased the operating time by about 30 min (17–40; median 29). A total of 702 lymph nodes were harvested and subjected to histopathological examination, with an average (SD) of 33.4 (9.6) lymph nodes dissected per patient (Table 2).

Five patients (23.8%) had unilateral sentinel drainage only. The frequency of sentinel drainage to the individual template regions is shown in Table 3. Taking the template regions (Figure 2) as the basis of analysis, 67 (38.3%) of 175 regions were NIRF-positive. Thirteen (7.4%) regions harbored lymph node metastases, all being fluorescent. A total of 42 hemipelves of lymph node were dissected. Of these, 37 (88.1%) were NIRF-positive, including seven (16.7%) with lymph node metastases.

TABLE 1a Patient characteristics and pathological findings.

Variable	
Gender	
Male, *n* (%)	17 (81)
Female, *n* (%)	4 (19)
Age	
Median (range)	63 (33–78)
Neoadjuvant therapy	
Neoadjuvant therapy, *n* (%)	4 (19)
No neoadjuvant therapy, *n* (%)	17 (81)
Pathological stage	
pT0, *n* (%)	2 (9.5)
pTis, pTa, *n* (%)	2 (9.5)
pT1, *n* (%)	1 (5)
pT2, *n* (%)	5 (24)
pT3, *n* (%)	10 (47)
pT4, *n* (%)	1 (5)
N-status	
pN0, *n* (%)	14 (67)
pN+, *n* (%)	7 (33)
Urinary diversion	
Ileal conduit, *n* (%)	16 (76)
Ileocoecal pouch, *n* (%)	1 (5)
Orthotopic neobladder, *n* (%)	4 (19)

TABLE 1b Histological subtypes of cystectomy specimen.

Histological subtype	*n* (%)
UC NOS	11 (52)
UC NOS + glandular type (minor)	1 (4.8)
UC NOS + SCC (minor)	2 (9.6)
SCC	1 (4.8)
SCC + UC NOS (minor)	1 (4.8)
Neuroendocrine + sarcomatoid + UC NOS (minor)	1 (4.8)
Plasmozytoid	1 (4.8)
pTis	1 (4.8)
pTa high grade	1 (4.8)
ypT0	1 (4.8)

Abbreviations: NOS, no other specified; SCC, squamous cell carcinoma; UC, urothelial carcinoma.

Regardless of the unit of analysis (template regions, and hemipelvis), we found no metastatic lymph nodes in NIRF-negative units. In one patient, two fluorescent nodes were identified outside the standardized template, which proved to be benign by histopathological examination.

TABLE 2 Frequency of sentinel drainage and metastatic involvement based on template regions, lymphnodes, and hemipelves.

Variable	
Sentinel drainage	
Unilateral, *n* (%)	5 (23.8)
Bilateral, *n* (%)	16 (76.2)
Template regions (TR)	
Resected TRs (%)	175 (100)
Sentinel TRs (%)	67 (38.3)
Metastatic TRs (%)	13 (7.4)
Lymph nodes (LN)	
Resected LN (%)	702 (100)
Sentinel LN (%)	313 (44.6)
Metastatic LN (%)	24 (3.4)
Hemipelves	
Resected hemipelves (%)	42 (100)
NIRF-pos. hemipelves (%)	37 (88.1)
Metastatic hemipelves (%)	7 (16.7)

Abbreviations: LN, lymph node; TR, template region.

TABLE 3 Frequency of localization of sentinel region detection.

Localization of sentinel template region	Frequency of sentinel region detection (%)
1: External iliac	21
2: Obturator fossa	39
3: Internal iliac	15
4: Presacral	15
5: Common iliac/aortic bifurcation	10

4 | DISCUSSION

Our aim was the reliable identification of clinically relevant templates to enable a more individualized, oncologically safe, and potentially less damaging lymphadenectomy in the future.

Lymphatic drainage in BC is complex and often bilateral. The pattern of lymphatic drainage is also influenced by malignant obstruction of the lymphatic vessels, chemotherapy, physical fitness, medication, and hydration status.[22] Several studies have already clinically tested SLN detection in BC, mainly using conventional techniques with technetium radiocolloid.[17,18,21,23–26]

Sherif et al. first described the sentinel procedure in BC.[23] In 2016, Polom et al. performed SLNB with preoperative hybrid SPECT/CT lymphoscintigraphy. Both methods showed a similar detection rate for sentinel nodes.[27] However, the disadvantage of all radio-guided sentinel methods is a high organizational effort with the involvement of different departments and radiation protection. In addition, the lack of intraoperative visualization of the SLNs in the topographical reference of the tissue requires cognitive fusion and/or radioguidance. Therefore, first experiences with a partly combined radio- and fluorescence-guided and partly exclusively fluorescence-guided sentinel procedure have been gained recently.[19,20,22] Indocyanine green (ICG) is usually used for this purpose. NIRF-technique enables the visualization of ICG in deeper tissue layers due to tissue penetration of the excitation light of several millimeters.[28] ICG binds to the proteins and lipids in lymphatic vessels, which leads to a more homogeneous distribution in lymphatic vessels and thus to a broader visualization in the tissue.[29] Manny et al. performed SNLB with unconjugated ICG in 10 patients undergoing robotic radical cystectomy and identified sentinel nodes in 9 of 10 patients, corresponding to a detection rate of 90%. ICG was injected cystoscopically circularly around the tumor. Another group reported 12 patients who received cystoscopic peritumoral injection of albumin bound ICG as part of SNLB in open radical cystectomy using the Mini-FLARE-camera- system. Sentinel nodes were identified in 11 of 12 patients. One lymph node metastasis was detected in a NIRF-negative lymph node, corresponding to a false-negative rate of 1 in 11.[22] Comparing the Mini-FLARE camera system to the device used in our study we see two main advantages of our system: the working distance of the Mini-FLARE is limited at 13 inches (=33 cm), and it is a static system requiring more equipment.[30] We therefore think that a handheld device improves flexibly in the operation situs and provides an easy and user-friendly setting maybe leading to a faster operation time (head-to-head comparison with our time was not possible because this data was not provided in this publication). Polom et al. analyzed a group of 50 patients who underwent open radical cystectomy with combined fluorescence- and radioguided SLNB. Sentinel nodes were detected using fluorescence guidance (unconjugated ICG) and technetium radiocolloid in 46 and 45 patients, respectively. Interestingly, fluorescence guidance detected more SLNs than radio guidance in 12 patients. In three patients, lymph node metastases were detected in NIRF-negative and radio-guidance-negative lymph nodes. The NIRF-camera used in this study was the Fluobeam (Fluoptics, France) providing a comparable setting to the device used in our study.[20]

Just like the aforementioned authors, we also performed peritumoral injection of ICG, as it is known that an intratumoral injection prevents intravascular transport of the dye due to the lack of lymphatic vessels in the tumor.[28]

Rietbergen et al. described the first hybrid tracer approach using Indocyanine Green–99mTc-Nanocolloid in 19 patients. Patients had robotic (12) or open (7) surgery. In the seven cases with open surgery the same device as in our study was used in combination with a gamma probe (Europrobe; Eurorad), for the robotic approach a laparoscopic gamma probe (Neoprobe; Johnson & Johnson Medical) with integrated NIRF-camera (Firefly) was used. In 2-day protocol patients first received the tracer via cystoscopy in the detrusor muscle 1 day before radical cystectomy followed by lymphoscintigraphy and SPECT/CT on the same day. The preoperative detection rate of sentinel nodes was 53% of which 90% could be identified intrasurgical with the gamma probe. Intraoperative use of fluorescence imaging was able to detect sentinel nodes in 58%. This pilot study reached a combined detection rate of 63% with 20% of the sentinel nodes outside the ePLND template. Of the four patients with metastatic lymph nodes two were visualized in preoperative imaging. Interestingly, the visualized sentinel nodes were the only sites of lymph metastasis. The metastatic nodes in the nonvisualized patients were found in the ePLND specimen. We think these findings support on the one hand that the visualization of sentinel nodes could lead to an oncological safe but at the same time individualized lymphadenectomy but also showed that ePLND was needed to find 50% of the lymph node metastasis in this cohort due to a (preoperative) nonvisualization rate of 47%. As the authors mentioned in their discussion better understanding of clinical and methodological aspects is needed to select those patients with the highest likelihood of sentinel node visualization. In our opinion, this combined approach would meet the requirement of an individualized and minimized lymphadenectomy but requires a very good patient selection to ensure the success of the procedure and to justify the effort in terms of clinical routine, patient comfort, and time/cost-effectiveness.

If a sentinel or lymphangiographic surgical procedure is to replace the standard template-based lymphadenectomy, it must first and foremost exclude false-negative sentinel nodes with the greatest possible certainty. Therefore, we decided to replace the SLN with a sentinel region based on the standard lymphadenectomy template (Figure 2). In case of fluorescence detection within a template region, the whole template region was dissected separately and pathologically evaluated. Fortunately, we were able to achieve a false negative rate of 0% in our 21 patients. 23.8% of patients had exclusively unilateral sentinel drainage. Since all lymph node metastases were localized in NIRF-positive sentinel template regions (38.3% NIRF positivity in lymph node regions), the resection of about 40% of standard templates may be sufficient and safe in the future after evaluation of larger collectives. In turn, we must accept a high false positive rate for a false negative rate of 0%. In addition, the comparatively long time from ICG application to detection of sentinel regions (75 min on average) may have contributed to prolonged migration of ICG in the lymphatic vessel. It is known that ICG binds to lipids and proteins in the lymphatic vessel and is transported as a complex. Under certain conditions, such as cancer or inflammation, cellular junctions can be remodeled, resulting in paracellular transport outside the lymphatic vessels. This in turn is significantly slower than the transport of a protein complex within the lymphatic vessel.[31] Another point to be mentioned is that we applicated ICG in the smooth muscle layer of the bladder wall which is in contrast to other authors using a fluorescent-guided approach whose application technique was (sub-)mucosal,[20,22] but the highest density of lymphatic vessels is found in the central zone of the smooth muscle layer.[32] This could indicate that the period of 75 min between application and detection as well as our technique led to a better distribution of the dye in all lymphatic channels.

The prolongation of the operation time by the applied procedure increases the probability for the occurrence of postoperative complications, which in this context must be critically regarded as a disadvantage of the procedure. In our opinion, there is no relevant optimization potential for the in-situ application itself, since the NIRF camera used is already a flexible handheld device. From the patient's point of view, we also consider an injection under local anesthesia before induction of anesthesia to be too stressful and therefore not advisable. In case of a negative sentinel region the operation time could be shortened due to a shorter lymphadenectomy and the time disadvantage of the procedure would be relativized. Ultimately, in our view, this point can only be conclusively clarified in further comparative studies.

Our study is subject to limitations. The monocentric study lacks a large sample, which is due to the feasibility character of the analysis. By applying the concept of lymph node region analysis, the pathologic finding details of the individual lymph nodes could not be related to ICG positivity. Furthermore, our study had a comparatively long period between ICG injection and detection. This certainly reduces the precision of the method, but in our opinion leads to an increased safety in finding and removing potentially tumor-bearing lymph nodes in the context of sentinel region analysis. Four patients were treated with NAC. As shown in a recent meta-analysis, the prognostic benefit of extended lymphadenectomy in terms of eradication of lymphonodular micrometastases could be reversed by such treatment.[5] Although detection of lymph node metastases is not the main goal of our work, this still has the potential to influence our results. At the same time, the fact that NAC could limit the extent of lymphadenectomy strengthens our template-based approach in terms of oncological safety. The lack of a standardized presentation of complication rates can be considered a weakness of the work. Lymphadenectomy differed from the standard approach only in that the NIRF-positive template was first identified as the sentinel region and resected. This was then followed by lymphadenectomy in the usual manner. Thus, from our point of view, there is no meaningful possibility for comparison. In the further development of our approach, a possible advantage of the "sentinel region only" resection in terms of reduced morbidity with equivalent oncological safety could be investigated in the future. This concept is supported by recent data from the SWOG1011 trial (NCT01224665), which found no oncological benefit (overall and disease-free survival) for ePLND versus PLND but showed higher complication rates (49% vs. 42%) and more than twice (19 vs. 7 patients) as many deaths 90 days postoperatively.[33]

5 | CONCLUSIONS

With fluorescence-guided dissection of sentinel regions, we were able to visualize tumor drainage pathways in all patients. While only representing 40% of the resected lymph nodes, the use of fluorescence guidance resulted in the resection of all tumor bearing nodes (false negative rate of 0%). In the future, after evaluation of larger collectives, resection of the fluorescent regions only may yield the desired outcome, while leading to a lower morbidity.

6 | PATIENT SUMMARY

Pelvic lymph node dissection is an integral part of radical cystectomy for BC but causes higher perioperative morbidity. Intraoperative identification of template regions with the highest likelihood of harboring metastases could reduce the extent of this procedure leading to less morbidity.

Therefore, we evaluated an intraoperative fluorescence-guided template region dissection using a handheld device for NIRF-guided surgery.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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