SEMMELWEIS EGYETEM

DOKTORI ISKOLA

Ph.D. értekezések

3350.

VIDA BALÁZS LAJOS

A szöveti adaptáció mechanizmusai

című program

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INNOVATIVE MANAGEMENT OF HPV-ASSOCIATED MALIGNANCIES IN GYNAECOLOGICAL ONCOLOGY

PhD thesis

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Budapest
2025

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List of Abbreviations

ASC-H	Atypical Squamous Cells – cannot exclude High-grade lesion
ASC-US	Atypical Squamous Cells of Undetermined Significance
ASCO	American Society of Clinical Oncology
BD	Blue Dye
BMI	Body Mass Index
CCRT	Concurrent Chemoradiotherapy
CI	Confidence Interval
CL	Complete Lymphadenectomy
DR	Detection Rate
EBRT	External Beam Radiotherapy
ESGO	European Society of Gynaecological Oncology
FIGO	Fédération Internationale de Gynécologie et d'Obstétrique
GDT	Guideline Development Tool
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HPV	Human Papillomavirus
hrHPV	High-Risk Human Papillomavirus
ICG	Indocyanine Green
κ (kappa)	Cohen's Kappa Statistic
LEEP	Loop Electrosurgical Excision Procedure
LVSI	Lymphovascular Space Invasion
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
NICU	Neonatal Intensive Care Unit
NIR	Near-Infrared
NACT	Neoadjuvant Chemotherapy
Pap test	Papanicolaou Test
pRb	Retinoblastoma Protein
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROSPERO	International Prospective Register of Systematic Reviews
R	R Programming Environment
RCT	Randomized Controlled Trial
RoB 2	Risk of Bias Tool for Randomized Trials (version 2)
ROBINS-I	Risk of Bias in Non-randomized Studies – of Interventions
SLN	Sentinel Lymph Node
SPIO	Superparamagnetic Iron Oxide
STI	Sexually Transmitted Infection
Tc99m	Technetium-99m
USPSTF	United States Preventive Services Task Force
WHO	World Health Organization

1. Introduction

1.1 The human papilloma virus (HPV) and its role in gynaecological cancers

Human papillomavirus (HPV) is a group of more than 200 related viruses, of which over 40 are known to infect the anogenital region.(1) HPV is primarily transmitted through sexual contact and is one of the most common sexually transmitted infections (STI) worldwide. While many HPV infections are transient and asymptomatic, persistent infection with certain high-risk HPV types is a critical factor in the development of several cancers, particularly gynaecological cancers.

HPV types are classified as low-risk or high-risk based on their oncogenic potential. Low-risk types, such as HPV 6, 11, 42 and 44 are generally associated with benign lesions like genital warts. In contrast, high-risk types, especially HPV 16, 18, 31, 33, 45, 52, and 58 are strongly associated with the development of malignancies. Among these, HPV 16 and 18 are the most prevalent, together accounting for approximately two-thirds of all HPV-related cervical cancer cases.(2) The high-risk HPV types are responsible for approximately 93% of cervical cancer cases globally, as well as a significant proportion of vulvar, vaginal, and anal cancers.(3)

The oncogenic mechanism of high-risk HPV involves the integration of viral DNA into the host genome, which leads to the overexpression of viral oncoproteins, most importantly, E6 and E7. These proteins interfere with critical tumour suppressor pathways, particularly those involving p53 and retinoblastoma protein (pRb).(2) The disruption of these regulatory pathways results in uncontrolled cellular proliferation, genomic instability, and ultimately malignant transformation.

Cervical cancer remains the most well-documented and prevalent HPV-related gynaecological malignancy. The strong etiological link between HPV infection and cervical cancer has led to the development of targeted prevention strategies, including HPV vaccination and routine cervical screening programs. The U.S. Preventive Services Task Force (USPSTF) suggests, women aged 21 to 29 should undergo cytology (Pap test) every three years. For women aged 30 to 65, screening options include primary high-risk HPV (hrHPV) testing every five years, co-testing with hrHPV and cytology every five years, or cytology alone every three years. Primary hrHPV testing is preferred due to its higher sensitivity for detecting high-grade lesions, although it may lead to increased follow-up procedures. Screening is not recommended for women under 21, those over 65 with adequate prior screening, or women who have undergone a hysterectomy with no history of high-grade precancerous lesions or cervical cancer. These

guidelines aim to balance the benefits of early detection with the potential harms of overdiagnosis and overtreatment. (4)

Vaccination against HPV is a cornerstone of primary prevention for cervical cancer. The American Society of Clinical Oncology recommends initiating routine immunization in children aged 9 to 14 with a two-dose schedule spaced at least six months apart, which has demonstrated strong immunogenicity and practicality across all resource settings. For individuals initiating vaccination at age 15 or older, a three-dose regimen is advised. The nonavalent vaccine covers high-risk HPV types 16, 18, 31, 33, 45, 52, and 58, while also protecting against types 6 and 11, which usually cause genital warts. Evidence indicates robust efficacy in preventing vaccine-type HPV infections and associated precancerous lesions, with sustained protection for at least five to ten years. Global guidelines, echoed by the WHO, prioritize girls aged 9–14 before sexual debut, with expanding strategies to include older adolescents and males to bolster herd immunity.(5) While vaccination provides great efficacy, it does not replace screening, therefore regular cervical screening remains essential even in vaccinated populations.

1.2 Assessing the Comparative Efficacy of Sentinel Lymph Node Detection Techniques in Vulvar Cancer: Protocol for a Systematic Review and Meta-Analysis

Vulvar cancer is considered a rare gynaecologic malignancy, accounting for approximately 5% of all cancers that originate in the female reproductive system and roughly 1% of total cancer diagnoses in women.(6) Although it is an uncommon condition, it carries serious clinical implications, particularly due to its prevalence among older women. Most diagnoses occur in individuals between 65 and 75 years of age, and encouragingly, a large portion of these cases are identified during the early stages of disease progression. This early detection contributes to improved patient outcomes.(7)

Survival rates for vulvar cancer are highly dependent on the stage at which the disease is diagnosed. For instance, when identified at Stage I, where the cancer remains localized and has not yet spread to lymph nodes or distant sites, the five-year survival rate is nearly 100%. However, the prognosis worsens significantly in more advanced stages, especially when the malignancy has metastasized to regional lymph nodes. In such cases, the five-year survival rate may decline below 60%, reflecting the more aggressive nature of advanced disease.(7, 8)

Historically, the standard surgical approach for staging and managing vulvar cancer included complete lymphadenectomy (CL), a procedure involving the removal of numerous lymph nodes

in the groin area. While effective in determining the extent of disease spread, CL is associated with a range of postoperative complications. These include the development of cysts containing lymph, lymphedema, dehiscence of the wound and chronic discomfort and pain, all of which can severely impact a patient's long-term quality of life. Given these drawbacks, the medical community sought alternative strategies that could provide accurate staging information while minimizing harm.(9)

One of the most significant innovations in this area has been the introduction of sentinel lymph node (SLN) mapping and biopsy. This approach enables clinicians to identify and remove only the first lymph node or nodes likely to be affected by metastasis, thereby avoiding the need for extensive node removal in cases where it may be unnecessary. For selected patients, particularly those with squamous cell carcinoma of the vulva, tumours less than 4 cm in size, unifocal lesions, and no clinical signs of lymph node involvement, the SLN technique has become a recommended standard of care.(9) The Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) supports the use of this approach in appropriately staged patients.(8)

Current protocols outlined by the European Society of Gynaecological Oncology (ESGO) provide more detailed technical guidance for performing SLN detection. These guidelines advocate the use of a radiotracer, commonly Technetium-99m (Tc99m) to help localize the sentinel lymph node. In addition to this, ESGO recommends combining the radiotracer with a secondary method to enhance visibility. This may involve the injection of a coloured dye, such as isosulfan blue or methylene blue, or the use of near-infrared imaging agents like indocyanine green (ICG). These dual-modality approaches increase the accuracy and reliability of SLN detection during surgery.(10)

1.3 Assessing the Comparative Efficacy of Sentinel Lymph Node Detection Techniques in Vulvar Cancer: a Systematic Review and Meta-Analysis

The concept behind SLN mapping is based on the anatomical and physiological principle that lymphatic drainage from a primary tumour site typically flows first to a specific lymph node, termed the sentinel node before spreading further. This node serves as a biological checkpoint, and if it is free of cancer, the likelihood of further nodal spread is markedly reduced. In recent years, SLN dissection has gained acceptance as a reliable, minimally invasive alternative to complete lymphadenectomy, especially in the context of vulvar squamous cell carcinoma. Numerous clinical studies have affirmed its safety and effectiveness, showing high detection and sensitivity rates with notably low false-negative results and minimal recurrence.(8-10)

Initially, the detection of sentinel nodes relied solely on BD, which, when injected near the tumour, visually marked lymphatic channels and potential sentinel nodes. While this approach was relatively straightforward, its diagnostic limitations became evident over time. Blue dye had a relatively narrow time interval of efficacy, generally between 30 and 60 minutes and required precise surgical timing for optimal visualization.(11-13) Consequently, it was largely replaced or supplemented by more reliable radiotracers such as Tc99m, a radioactive isotope with a superior detection profile. Tc99m, used in conjunction with lymphoscintigraphy and intraoperative gamma probes, became a cornerstone of SLN procedures due to its improved localization capabilities.(11, 14-16)

Contemporary guidelines from both the ESGO and the National Comprehensive Cancer Network (NCCN) now advocate a dual-tracer approach, combining Tc99m with a visual dye, either BD or an imaging agent like ICG.(10, 17) This combination enhances the likelihood of successful node identification and reduces the risk of overlooking metastatic involvement. However, despite its diagnostic strength, the use of Tc99m presents practical drawbacks. It requires coordination with nuclear medicine departments, specialized facilities, and preoperative injection scheduling. Additionally, it does not offer direct visual confirmation of lymphatic pathways during surgery, which can be a challenge in some operative settings.(18, 19)

In contrast, ICG has emerged as a compelling alternative, especially when used with near-infrared (NIR) imaging systems. This fluorescent dye provides real-time visual feedback during surgery and can be administered intraoperatively, streamlining the procedure into a single, unified surgical event. Its hydrophilic nature and relatively low toxicity profile make it an attractive option, and several studies have shown it to deliver high detection rates comparable to, or even exceeding, traditional techniques. The main downside of ICG is its price, which makes it unfeasible in some parts of the world.(20)

Another innovative advancement in this field is the application of superparamagnetic iron oxide (SPIO) as a method for SLN detection. This procedure employs magnetic nanoparticles that can be visualized preoperatively via magnetic resonance imaging (MRI) and detected intraoperatively using handheld magnetometers.(21) The SPIO approach eliminates the need for radioactive materials, making it particularly advantageous in clinical environments where radiation safety concerns or logistical constraints limit the use of isotopes. Preliminary findings

indicate that SPIO achieves high detection rates and offers a practical, non-radioactive alternative, which may support broader implementation in various healthcare settings.(22, 23)

1.3.1 The role of the sentinel lymph node mapping in cancer

The theoretical and clinical foundation of SLN mapping lies in a well-established anatomical and physiological principle concerning lymphatic drainage pathways. Specifically, lymphatic fluid originating from a primary tumour site does not disseminate randomly throughout the lymphatic system but rather follows a relatively orderly and predictable route. The first lymph node or group of nodes that receives lymphatic drainage directly from the tumour is designated as the sentinel lymph node. This node serves as the initial biological barrier or checkpoint within the lymphatic network that tumour cells must traverse during the metastatic process.(24)

The conceptualization of the SLN in the metastatic cascade was initially developed in the context of melanoma and subsequently adapted to various solid tumours, including breast, vulvar, cervical, and penile cancers, among others.(25) The principle asserts that if the sentinel node is histologically free of metastatic cancer, then the probability of metastasis in more further lymph nodes is exceedingly low. This has been substantiated in numerous clinical studies demonstrating that the status of the SLN accurately predicts the condition of the entire regional lymphatic basin in the majority of cases.(9, 26-28)

From a pathophysiological perspective, the lymphatic system acts as a conduit for tumour cell dissemination, but its architecture comprising afferent lymphatic channels, lymph nodes, and efferent vessels is such that metastatic spread usually follows a sequential progression. The SLN thereby represents the initial site of potential colonization by malignant cells. Histopathological examination of the SLN thus offers a highly sensitive and specific means of assessing the nodal status without necessitating extensive lymphadenectomy, which carries substantial morbidity, including lymphedema, nerve injury, and infection.(29, 30)

Moreover, the clinical utility of SLN biopsy extends beyond mere staging; it also provides prognostic information and may guide adjuvant therapy decisions. The absence of tumour cells in the SLN often obviates the need for more radical surgical interventions, aligning with the contemporary paradigm of minimally invasive oncological surgery. Consequently, SLN mapping has become a cornerstone technique in surgical oncology, supported by a growing body of evidence from prospective trials and meta-analyses affirming its diagnostic accuracy, prognostic value, and safety profile.(8, 10, 31)

1.3.2 Currently practiced methods of SLN detection in vulvar cancer

Sentinel lymph node detection plays a pivotal role in the surgical management of early-stage vulvar cancer. Accurate identification of SLNs enables targeted lymphadenectomy, thereby reducing the morbidity associated with full inguinofemoral lymph node dissection. Over the past two decades, several SLN mapping techniques have been developed and refined, each offering distinct advantages in terms of DR, surgical guidance, and clinical practicality.(27)

The earliest method employed for SLN detection was the use of BD. This technique involves injecting a water-soluble dye, such as isosulfan blue or methylene blue into the peritumoral area approximately 30 to 60 minutes prior to surgery. The dye travels through the lymphatic channels, staining the SLN and allowing it to be identified visually during the operation. This method is straightforward, cost-effective, and requires no specialized equipment. However, its major limitation lies in its relatively low detection rate when used as a sole agent. Additionally, BD is associated with risks such as allergic reactions and inconsistent lymphatic uptake, particularly in patients with altered lymphatic drainage due to prior surgery or radiation.(25, 32, 33)

To improve SLN localization, Tc99m and Tc99m labelled nano-colloids were introduced as a radioactive tracer method. The tracer is injected peritoumorally, typically on the day before surgery, and its uptake by lymph nodes is tracked preoperatively using lymphoscintigraphy. Intraoperatively, a handheld gamma probe is used to localize the radioactive SLN. Although this technique does not offer visual identification, it significantly improves detection rates when used alone or in combination with blue dye. In vulvar cancer, the dual technique (Tc99m + BD) has become a widely accepted standard, demonstrating both high sensitivity and low false-negative rates in appropriately selected patients with unifocal tumours <4 cm and clinically negative groins. However, the requirement for nuclear medicine infrastructure and exposure to ionizing radiation remain drawbacks.(34-38)

In recent years, ICG has gained attention as a novel SLN tracer. ICG is a fluorescent dye that is injected into the peritumoral region shortly before surgery. Using NIR imaging systems, the dye can be visualized in real-time as it migrates through the lymphatic system and accumulates in SLNs. ICG offers high detection rates comparable to traditional methods and provides the added benefit of visual guidance, which can enhance surgical precision. Early studies in vulvar cancer have demonstrated promising results with ICG, particularly when combined with

radioactive tracers, although it has not yet fully replaced standard techniques in clinical guidelines.(15, 39-41)

The most recent advancement in SLN mapping is the use of SPIOs. These magnetic tracers are injected into the tumour or peritumoral tissue at least a few hours prior to surgery and accumulate in SLNs, where they can be detected intraoperatively using a handheld magnetic probe. Although SPIO does not offer visual guidance, its detection rate has been shown to be comparable to radiocolloids. Moreover, SPIO offers several logistical advantages: it does not involve radiation, it allows for flexible injection timing (even several days prior to surgery), and it eliminates the need for nuclear medicine facilities. Initial clinical studies in gynaecologic oncology, including vulvar cancer, suggest that SPIO may be a viable alternative or adjunct to existing methods, though its adoption is still in early phases.(21-23, 42-45)

1.4 Cervical Cancer During Pregnancy: A Multidisciplinary Approach to a Complex Oncological Case

Cervical cancer remains one of the most prevalent malignancies affecting women globally, ranking fourth in incidence and mortality. It is most often associated with persistent infection by high-risk strains of HPV, particularly types 16 and 18.(46) Through screening programs that include cytological examination and HPV testing, many cases are now detected at precancerous or early stages, which has significantly improved treatment outcomes. However, when cervical cancer is diagnosed during pregnancy, it presents an intricate therapeutic dilemma, demanding a delicate balance between maternal health and foetal safety.

The incidence of cervical cancer during pregnancy is ranging from 0.44 to 5.08 per 100,000 pregnancies, and the incidence of malignancies diagnosed during pregnancy is expected to rise due to the increasing trend of delayed childbearing.(47) The coexistence of cancer and pregnancy introduces a multifaceted challenge, both clinically and ethically. Management requires a careful balance between optimal oncologic care and foetal preservation, often within a multidisciplinary framework involving oncologists, obstetricians, neonatologists, and surgeons. Given the ethical dilemmas and the absence of prospective trials, clinical evidence relies largely on case reports and series, which remain essential for informing individualized treatment strategies. This personalization requires input from a multidisciplinary team including gynaecologic oncologists, obstetricians, neonatologists, and other specialists, with the patient and family playing a central role in decision-making.(48, 49)

Standard diagnostic procedures, such as cytology, HPV typing, colposcopy, and imaging must be adapted during pregnancy, due to limitations in the use of ionizing radiation. While pelvic MRI and ultrasound remain safe and effective diagnostic tools, staging and treatment planning are constrained. Surgical interventions, such as conization or sentinel lymph node biopsy, can be cautiously performed during the early second trimester if indicated, although they carry elevated risks of pregnancy complications, including miscarriage and preterm labour.(48)

2. Objectives

The accurate staging of vulvar cancer is essential for determining prognosis and guiding treatment decisions, particularly the evaluation of inguinal lymph node involvement. SLN biopsy has emerged as a reliable and less morbid alternative to complete lymphadenectomy for early-stage vulvar cancer. The optimal method for SLN detection remains an evolving area of research, with various tracers, such as Tc99m, blue dye, ICG, and SPIO being employed in clinical practice, either alone or in combination. Each of these techniques offers distinct advantages and limitations in terms of detection rate, visual guidance, cost, logistical feasibility, and safety.

1. The protocol of our meta-analysis aims to form a robust methodological foundation for the meta-analysis, making it transparent and scientifically acceptable. We aim to set the criteria, methodological rigor, statistical foundation and overall design of the analysis, for which we can adhere later.

2. The primary goal is to conduct a comprehensive systematic review and meta-analysis to compare the DRs of these SLN mapping methods in patients with vulvar cancer. A key objective is to determine whether newer agents such as ICG and SPIO can match or surpass the performance of the currently recommended standard combinations, namely Tc99m with blue dye or ICG. We aim to assess and compare both per-patient and per-groin detection rates across all identified studies, using robust statistical models that account for heterogeneity in study designs, patient populations, and tracer combinations. By analysing data from a large pool of studies, including randomized controlled trials and observational cohorts, this research seeks to generate high-certainty evidence to support or refine current guideline recommendations, such as those from ESGO and NCCN.

3. In addition to detection rates, this study also seeks to explore secondary objectives such as the influence of patient demographics (e.g., mean age and body mass index), the variability in tracer dose and concentration, and the impact of tracer combinations on detection efficacy. Special attention is given to emerging technologies like SPIO, which, despite being less studied, may offer significant logistical and clinical benefits over conventional methods, including radiation-free usage and MRI compatibility.

Although clinical guidelines exist for the management of HPV-associated malignancies within the field of gynaecological oncology, several aspects of this domain remain insufficiently investigated. One such area is the management of cervical cancer during pregnancy, a relatively rare clinical scenario for which high-quality, population-based evidence is limited. As a result, current guidelines often lack definitive recommendations and instead defer to clinician judgment. However, given the rarity of these cases, many practitioners may have limited direct experience, potentially complicating decision-making processes. In light of these limitations within the existing clinical guidelines, particularly the scarcity of robust, evidence-based recommendations for managing cervical cancer during pregnancy, there is a clear need to consolidate and critically assess the current body of literature.

4. The primary objective of this research is to examine the clinical decision-making process in managing cervical cancer during gestation, using a detailed case study as a foundation for analysis. The case of a 32-year-old woman diagnosed with cervical cancer during early pregnancy and treated with neoadjuvant chemotherapy followed by preterm caesarean section and radical hysterectomy will be used to illustrate key concepts. Through this analysis, the article seeks to identify both the strengths and limitations of current protocols, assess oncological and obstetric outcomes, and highlight areas in need of further clinical guidance.

5. Another aim of this work is to evaluate the timing, safety, and efficacy of therapeutic interventions, particularly sentinel lymph node mapping, chemotherapy administration, and surgical treatment within the unique context of pregnancy. Special focus will be given to the role of sentinel lymph node biopsy and pelvic lymphadenectomy using minimally invasive, robot-assisted techniques, which are increasingly used to guide treatment planning and reduce surgical morbidity. The thesis will also examine the impact of tumour progression under neoadjuvant therapy, the implications of foetal maturity in scheduling delivery, and the coordination of perinatal care to minimize neonatal morbidity.

6. Furthermore, this research intends to underscore the importance of personalized treatment planning based on tumour stage, gestational age, and patient preference. It also investigates the collaborative role of a multidisciplinary team, including

oncologists, obstetricians, neonatologists, radiologists, and pathologists in optimizing both maternal and foetal outcomes.

3. Methods

3.1 Assessing the Comparative Efficacy of Sentinel Lymph Node Detection Techniques in Vulvar Cancer: Protocol for a Systematic Review and Meta-Analysis

3.1.1 Registration

To ensure transparency, reproducibility, and methodological rigor, a protocol was developed and registered in advance of conducting the systematic review and meta-analysis. The protocol, titled "Assessing the Comparative Efficacy of Sentinel Lymph Node Detection Techniques in Vulvar Cancer", was designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement and Cochrane Handbook for Systematic Reviews of Interventions. It was registered on the International Prospective Register of Systematic Reviews (PROSPERO) under the ID CRD42024590774, thereby fulfilling key international standards for pre-defining the objectives, methodology, and outcomes of systematic reviews.

3.1.2 Comparison of interventions

The protocol outlines a comprehensive plan to assess and compare the diagnostic performance of multiple SLN detection methods in patients diagnosed with vulvar cancer. Specifically, it aims to evaluate DRs across the most commonly used techniques: Tc99m, ICG, blue dye, and SPIO. Given the clinical importance of minimizing surgical morbidity while ensuring oncologic safety, the protocol prioritizes comparison of these techniques in terms of per-patient and per-groin detection efficacy.

3.1.3 Selection of the studies

The inclusion criteria target studies involving women with histologically confirmed vulvar squamous cell carcinoma, primarily in FIGO stages T1a to T2, where tumours are unifocal, ≤4 cm in size, and without clinical evidence of nodal involvement. Eligible studies include randomized controlled trials, prospective and retrospective observational studies, without restriction on publication language or geographic origin.

3.1.4 Ethical considerations

Importantly, the protocol specifies that no original patient data will be collected, and as such, no ethical approval is required. Nonetheless, the review will follow ethical research principles by ensuring accurate representation and citation of all included studies.

3.2 Assessing the Comparative Efficacy of Sentinel Lymph Node Detection Techniques in Vulvar Cancer: a Systematic Review and Meta-Analysis

3.2.1 Eligibility Criteria

A comprehensive inclusion framework was established using the Population–Intervention–Comparison–Outcome (PICO) format. Eligible studies involved adult female patients diagnosed with vulvar cancer who underwent SLN biopsy as part of either their diagnostic workup or therapeutic management. Interventions and comparisons included various SLN detection tracers: Tc99m, ICG, SPIO, blue dye, and combinations such as Tc99m with BD or ICG. The primary outcome of interest was the detection rate (DR), defined as the proportion of successfully identified sentinel lymph nodes either per patient or per groin.

Both randomized controlled trials and observational studies were considered for inclusion, provided they contained extractable data on detection rates for at least one SLN technique.

3.2.2 Search Strategy and Information Sources

An exhaustive literature search was executed using multiple databases, including PubMed (MEDLINE), Embase, Web of Science, Cochrane CENTRAL, and Scopus, covering all records up to August 15, 2024. The search terms applied were intentionally broad to maximize sensitivity, with the main search string being: "vulv* AND sentinel", applied across all searchable fields. No language or publication status restrictions were imposed.

3.2.3 Study Selection and Data Extraction

Following deduplication, articles were screened independently by two reviewers using a two-tiered process: initial title and abstract screening, followed by full-text evaluation. Any discrepancies in inclusion decisions were resolved by discussion or by consulting a third senior reviewer. To ensure safe, blinded and transparent management, reference management softwares were utilized, such as EndNote X9, and Rayyan.ai for screening. Inter-reviewer reliability was quantified using Cohen’s kappa, achieving substantial agreement.

Data were meticulously extracted by two reviewers using a structured form, capturing study design, year of publication, population size, intervention specifics, and SLN detection outcomes. Where reported, detection rates were extracted separately on a per-patient and per-groin basis to account for methodological differences in how outcomes were calculated. For

studies evaluating midline tumours, bilateral groin detection data were particularly emphasized due to the surgical importance of comprehensive lymph node assessment in such cases.

3.2.4 Risk of Bias and Quality Appraisal

Risk of bias was independently evaluated by two reviewers using the ROBINS-I tool for non-randomized studies and the RoB 2 tool for randomized controlled trials. Disagreements were reconciled by a third reviewer. The quality of evidence for each outcome was assessed using the GRADE approach, facilitated through the GRADEpro GDT software, focusing on elements such as study design, inconsistency, imprecision, indirectness, and publication bias. The certainty of evidence was categorized as high, moderate, low, or very low, with an emphasis placed on clinically critical outcomes.

3.2.5 Statistical Analysis and Data Synthesis

Due to the anticipated heterogeneity in study populations and tracer modalities, all meta-analytic models were constructed using a random-effects framework. Detection rates and corresponding 95% confidence intervals (CIs) were used as the primary effect measures. A three-level multivariate meta-analysis model was employed to account for inter-study correlations, particularly in studies evaluating multiple detection techniques on either overlapping or distinct patient cohorts.

To complement this, a classical two-level random-effects model was also conducted, primarily to assess the influence of individual studies, heterogeneity, and potential publication bias. For this purpose, funnel plots and Peters' test (a modified version of Egger's test) were employed, provided the number of studies was sufficient ($n \geq 10$).

Potential outliers and influential studies were identified using standardized influence diagnostics, as outlined in Harrer et al.'s methodological guide. All statistical analyses were carried out using the R statistical environment. Key packages included "meta", "dmetar", and "metafor" for meta-analysis modelling, and "ggplot2" for data visualization.

3.2.6. The calculation of Cohen's Kappa

In line with the methodological principles outlined in the Cochrane Handbook for systematic reviews and meta-analyses, inter-rater reliability was assessed to ensure transparency and reproducibility during the study selection process. To quantify agreement between independent

reviewers, Cohen's kappa statistic (κ) was employed at two critical stages: first, following the screening of titles and abstracts, and second, after the evaluation of full-text articles. This statistical measure compares the degree of concordance between reviewers to the level of agreement expected by chance alone. The κ coefficient is derived using the formula:

$$\kappa = \frac{p_0 - p_e}{1 - p_e},$$

where Po represents the proportion of actual agreement between raters, and Pe denotes the probability of random agreement. The observed agreement (Po) is calculated by adding the number of instances where both reviewers made the same decision (i.e., diagonal values in a 2×2 matrix) and dividing this sum by the total number of assessed items.

3.3 Cervical Cancer During Pregnancy: A Multidisciplinary Approach to a Complex Oncological Case

This case study was conducted as a retrospective clinical analysis of a patient diagnosed and treated for cervical cancer during pregnancy. The report followed a multidisciplinary model of care at two major medical institutions in Hungary: the Department of Obstetrics and Gynaecology at Semmelweis University and the National Institute of Oncology, Budapest. All diagnostic, therapeutic, and surgical interventions adhered to institutional protocols and international guidelines, with patient safety and ethical standards rigorously observed.

3.3.1 Patient Identification and Initial Assessment

The patient, a 32-year-old gravida was initially identified through routine gynaecological screening in December 2023, prior to conception. Cytological examination using liquid-based Pap smear testing yielded an ASC-H (Atypical Squamous Cells – cannot exclude High-grade lesion) result. A subsequent colposcopic assessment did not indicate visible pathology, and a follow-up cytology conducted three months later again returned an ASC-H result. These findings prompted further virological and molecular testing, including HPV genotyping and methylation analysis. The patient tested positive for high-risk HPV genotype 18, and methylation markers indicated epigenetic activity consistent with malignant transformation. However, immunocytochemical staining for p16/Ki-67 was negative, prompting a conservative follow-up approach.

3.3.2 Diagnosis During Pregnancy

In May 2024, the patient presented for confirmation of pregnancy. During initial obstetric evaluation, an additional cytological sample was collected, which revealed glandular epithelial neoplasia. This result triggered urgent diagnostic escalation. A loop electrosurgical excision procedure (LEEP conization) was performed under local anaesthesia. Histopathological evaluation of the excised specimen revealed grade 3 squamous cell carcinoma with high-risk HPV association and the absence of lymphovascular space invasion (LVSI).

3.3.3 Radiological Staging

Following histological confirmation of malignancy, staging was conducted via MRI of the pelvis. MRI revealed a cervical mass, 30 mm in diameter, confined to the cervix, without evidence of parametrial invasion or lymph node involvement. Although, imaging did not indicate pathological lymphadenopathy, radiological techniques have limited negative predictive value for micrometastases. Therefore, surgical lymph node evaluation was recommended by the institutional oncology board of the National Institution of Oncology.

3.3.4 Surgical Staging Procedures

At 16 weeks of gestation, the patient underwent a robot-assisted laparoscopic sentinel lymph node biopsy and bilateral pelvic lymphadenectomy. In total, 28 lymph nodes were excised and submitted for pathological assessment, including definitive histopathology; all were negative for metastasis. These procedures were performed under general anaesthesia using da Vinci-assisted laparoscopy, with continuous intraoperative foetal monitoring and anaesthesiology oversight.

3.3.5 Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Semmelweis University. Informed consent for treatment and publication was obtained from the patient. The care pathway adhered to national and international standards for oncologic care in pregnancy.

4. Results

4.1 Assessing the Comparative Efficacy of Sentinel Lymph Node Detection Techniques in Vulvar Cancer: Protocol for a Systematic Review and Meta-Analysis

4.1.1 Expected results

While this section presents a predefined protocol rather than empirical findings, it offers a structured projection of anticipated outcomes grounded in current evidence and methodology. The following section presents these expected results, offering insight into the potential implications of the planned analysis. In the systematic review and meta-analysis, we anticipate several key findings related to the comparative efficacy of different SLN detection techniques employed in the surgical management of vulvar cancer. Given the established literature and preliminary observational data, we expected to observe notable variability in DRs across individual tracers and their combinations. Specifically, dual-modality approaches such as Tc99m combined with BD or ICG are likely to demonstrate superior per-patient and per-groin detection rates when compared to single-agent methods.

Based on previous reports, Tc99m was expected to yield high detection rates exceeding 90%, especially when used in conjunction with a visual tracer. As such, this review aimed not only to confirm the efficacy of Tc99m but to highlight whether newer or more accessible alternatives provide comparable performance.

We anticipated that ICG, would demonstrate high detection rates, potentially on par with Tc99m while offering practical advantages such as real-time intraoperative visualization and reduced preparation time. Previous studies suggest that ICG-guided SLN mapping may achieve detection rates comparable to dual-tracer methods, and the present review is expected to confirm or challenge this observation through pooled estimates.

Another focus of this analysis was the emerging SPIO technique. Although SPIO has not been widely adopted yet, early results from limited studies suggest that it may offer detection rates similar to radiotracers while circumventing the need for radiation. Given its logistical advantages, such as flexible injection timing and independence from nuclear medicine infrastructure, SPIO was expected to show potential as a viable alternative, especially in resource-constrained environments.

With regard to BD, we expected to confirm its inferior performance as a standalone tracer. The review is likely to reinforce the notion that blue dye alone lacks the sensitivity required for optimal SLN mapping and is most effective only when used in combination with other tracers.

Secondary analyses explored how patient-specific and procedural variables, such as mean age, BMI, tumour size, and tracer dose affect detection outcomes. While such data may be inconsistently reported across studies, we anticipated discovering trends that inform patient selection and procedural standardization in SLN detection.

4.2 Assessing the Comparative Efficacy of Sentinel Lymph Node Detection Techniques in Vulvar Cancer: a Systematic Review and Meta-Analysis

4.2.1 Study selection

A comprehensive and systematic literature search was conducted across multiple electronic databases, which initially returned a total of 1,418 potentially relevant articles. These records were compiled and imported into EndNote for the first stage of processing. After the removal of duplicate entries, identified through both automated and manual screening, a total of 967 unique studies remained for further evaluation.

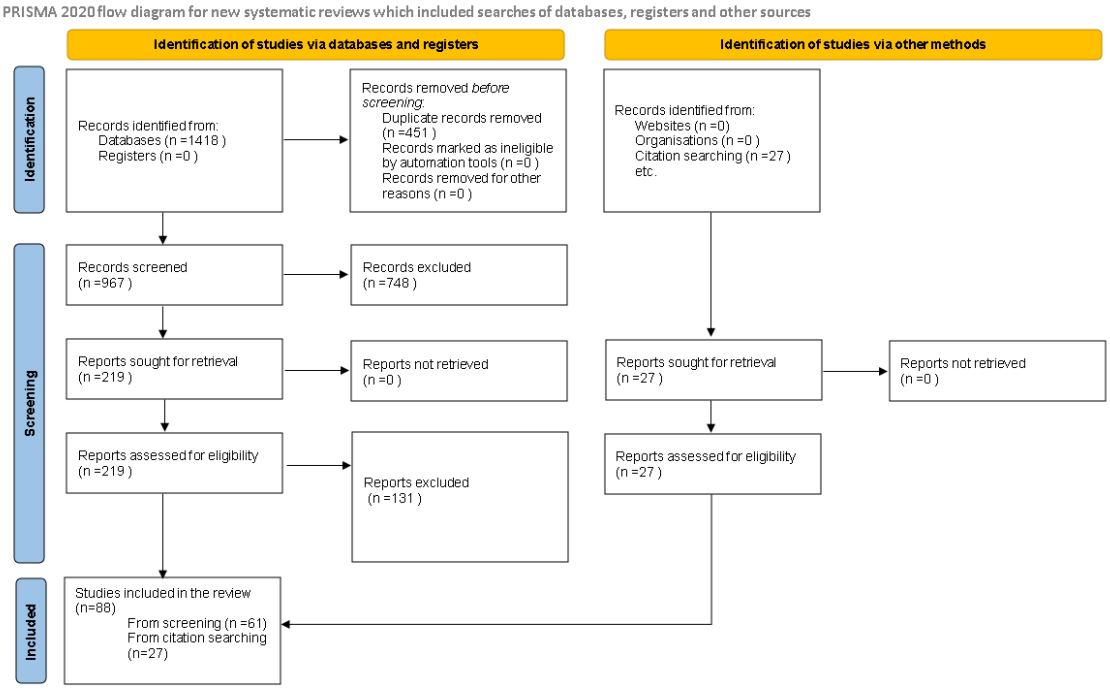
The screening of titles and abstracts was then performed independently by two reviewers according to pre-established inclusion and exclusion criteria outlined in the registered protocol. This step led to the elimination of 748 publications that did not meet the predefined criteria, either due to irrelevance to the topic, inappropriate study design, or a lack of data regarding SLN detection in vulvar cancer. Consequently, 219 articles proceeded to the full-text review phase.

Upon full-text assessment, a more detailed evaluation of study eligibility was performed. Of these, 94 articles were deemed potentially suitable based on their alignment with the review's scope and their provision of relevant outcome data. During the data extraction process, however, 6 additional articles were excluded due to either missing or inconsistent data, a lack of clarity in methodology, or failure to meet specific inclusion thresholds such as patient population, tracer type, or outcome reporting quality.

The final result of this rigorous selection process was the inclusion of 61 articles for analysis: 59 observational studies and 2 randomized controlled trials (RCTs). To ensure comprehensiveness and reduce the risk of publication bias, a citation tracking process was also conducted. Reference lists of relevant systematic reviews and meta-analyses were screened

manually, which led to the identification of an additional 27 observational studies that met all inclusion criteria and were subsequently added to the dataset.

In total, the final review and meta-analysis encompassed 88 studies, comprising both interventional and non-interventional research. These studies collectively involved 4,637 patients, making this one of the most comprehensive analyses to date on SLN detection techniques in vulvar cancer. The detailed flow of the study selection process is illustrated in Figure 1, following the PRISMA 2020 guidelines.



1. Figure Flow diagram for the selection process

4.2.2 Characteristics of the included studies

Among the 88 studies included in this systematic review and meta-analysis, a diverse array of SLN detection methods were investigated, with many studies evaluating more than one technique. This comprehensive analysis revealed substantial variation in the choice and combination of tracers used across studies, reflecting both historical trends and the ongoing evolution of clinical practice in vulvar cancer surgery.

A total of 34 studies evaluated the efficacy of blue dye as a single-agent tracer for SLN detection. These studies encompassed various formulations such as isosulfan blue and methylene blue, used either alone or in combination with other agents.

Tc99m, a radiotracer regarded as the traditional gold standard for SLN mapping in vulvar cancer, was examined in 55 studies. These studies covered both planar lymphoscintigraphy and intraoperative gamma probe detection, either as standalone Tc99m or in combination with adjunct agents. Given the widespread endorsement of Tc99m in international guidelines, its prevalence among the included studies was expected and reinforces its foundational role in SLN detection strategies.

ICG, a fluorescent tracer visualized intraoperatively through near-infrared imaging systems, was assessed in 16 studies. The studies investigating ICG frequently explored its standalone use as well as its performance when combined with other tracers.

A smaller subset of 3 studies evaluated SPIO, a newer magnetic tracer used for SLN detection. Although relatively limited in number, these studies represent a growing interest in non-radioactive and flexible detection systems that avoid the logistical challenges of radiopharmaceuticals.

In addition to studies assessing single-agent techniques, many investigations explored combinations of tracers to improve detection rates and reliability. Notably, 32 studies investigated the dual-agent combination of Tc99m and blue dye, a widely accepted strategy in many institutions due to its complementary mechanisms.

Similarly, 12 studies examined the performance of the Tc99m and ICG combination, integrating radio-guidance with near-infrared visualization to enhance intraoperative accuracy.

It is important to emphasize that many of the included studies evaluated multiple SLN detection techniques within the same cohort or across subgroups, allowing for direct or indirect comparisons of tracer performance. This diversity in methodology enriches the comparative scope of the present analysis but also introduces complexity in interpreting pooled results. The overlap between techniques also reflects real-world clinical practice, where decisions regarding tracer selection often depend on institutional capabilities, surgeon preference, and patient-specific factors.

A detailed summary of the methodological characteristics of the included studies, including tracer types, study design, sample sizes, and key patient demographics such as age, body mass index (BMI), and tumour staging, is presented in Table 1. This tabulated data provides a foundation for the quantitative synthesis and subgroup analyses described in the subsequent sections of this chapter.

Table 1. Basic characteristics of the included studies.

Study	Event	Number	SLND Method	Detection Method	Age	BMI	Study Design	ICG Concentration	ICG Volume	Activity
Guijarro-Campillo, 2024 (50)	64	75	PP	Tc99m	67,49	27,77	P	-	-	120
	62	75	PP	ICG	67,49	27,77	P	2,5	5	-
Del Valle, 2024 (21)	18	18	PP	Tc99m	67,20	26,10	P	-	-	-
	18	18	PP	SPIO	67,20	26,10	P	-	-	-
Rundle, 2023 (13)	56	96	PG	Tc99m+Bd	61,00	26,40	P	-	-	40
	73	96	PG	Tc99m	61,00	26,40	P	-	-	40
	75	96	PG	ICG	61,00	26,40	P	0,25	1	-
	59	96	PG	Bd	61,00	26,40	P	-	-	-
	81	96	PG	Tc99m+ICG	61,00	26,40	P	0,25	1	40
Kwong, 2023 (12)	67	71	PG	Tc99m	64,00	-	P	-	-	40
Garrett, 2023 (51)	142	164	PP	Tc99m+Bd	66,40	-	R	-	-	10
Cornel, 2023 (52)	283	303	PG	Tc99m+Bd	66,00	28,80	R	-	-	-
	36	40	PG	Tc99m+ICG	68,00	28,40	R	-	-	-
	20	22	PG	ICG	68,00	28,40	R	-	-	-
Frøding, 2022 (53)	97	100	PP	Tc99m+ICG	-	-	P	-	-	-

Fais, 2022 (54)	7	7	PP	ICG	73,00	-	R	-	-	-
	2	2	PP	Tc99m+ICG	73,00	-	R	-	-	-
Siegenthaler, 2021 (40)	56	64	PG	ICG	71,00	27,85	R	2,5	8,4	-
	52	58	PG	Tc99m	71,00	27,85	R	-	-	60
	7	9	PG	Bd	71,00	27,85	R	-	-	-
	56	58	PG	Tc99m+ICG	71,00	27,85	R	2,5	8,4	60
Huerta Martín, 2021 (42)	12	12	PP	Tc99m	65,40	-	P	-	-	-
	12	12	PP	SPIO	65,40	-	P	-	-	-
Prader, 2020 (15)	61	64	PG	Tc99m	69,00	26,00	R	-	-	180
	56	64	PG	ICG	69,00	26,00	R	1,25	20	-
Jedryka, 2020 (43)	20	20	PP	Tc99m	74,80	32,30	P	-	-	-
	20	20	PP	SPIO	74,80	32,30	P	-	-	-
Deken, 2020 (39)	35	38	PP	Tc99m+Bd	71,00	28,00	RCT	-	-	-
	35	36	PP	Tc99m+ICG	68,00	28,20	RCT	0,125	2	-
Orta, 2020 (55)	41	55	PG	Tc99m	72,00	-	R	-	-	148,00
Piechowicz, 2020 (56)	54	55	PP	Tc99m	72,00	-	P	-	-	-

	51	55	PP	Bd	72,00	-	P	-	-	-
Zekan, 2019 (16)	34	34	PP	Tc99m	-	-	P	-	-	-
Siegenthaler, 2019 (41)	48	55	PG	ICG	-	-	R	-	-	-
	37	44	PG	Tc99m	-	-	R	-	-	-
	7	9	PG	Bd	-	-	R	-	-	-
	42	44	PG	Tc99m+ICG	-	-	R	-	-	-
Paskeviciute Frøding, 2019 (57)	54	58	PG	Tc99m+ICG	-	-	P	-	-	-
Klat, 2019 (58)	84	86	PP	Tc99m+Bd	-	-	P	-	-	-
Kashi, 2019 (59)	10	10	PP	ICG	-	-	P	2,5	0,75	-
Broach, 2019 (60)	2	2	PG	Tc99m	-	-	R	-	-	-
	26	27	PG	ICG	-	-	R	-	-	-
	3	3	PG	Bd	-	-	R	-	-	-
	101	110	PG	Tc99m+Bd	-	-	R	-	-	-
	96	96	PG	Tc99m+ICG	-	-	R	-	-	-
	3	3	PG	ICG+Bd	-	-	R	-	-	-
Sykes, 2019 (61)	111	113	PP	Tc99m+Bd	64,00	-	P	-	-	-
Ricciuti, 2018 (62)	112	132	PG	Tc99m+Bd	65,60	-	R	-	-	-

Soergel, 2017 (63)	52	52	PG	Tc99m	63,00	-	P	-	-	10
	52	52	PG	ICG	63,00	-	P	1,25	20	-
	15	36	PG	Bd	63,00	-	P	-	-	-
Bharathan, 2017 (64)	32	32	PP	Tc99m	67,00	28,60	P	-	-	-
	31	32	PP	Bd	67,00	28,60	P	-	-	-
van Doorn, 2016 (65)	21	27	PP	Tc99m+Bd	65,30	-	R	-	-	75
	37	44	PG	Tc99m+Bd	65,30	-	R	-	-	75
Verbeek, 2015 (66)	12	12	PP	Tc99m+ICG	72,00	24,00	P	0,12	1	80
Laios, 2015 (67)	10	11	PP	ICG	61,60	-	P	5	4	-
Bogliolo, 2015 (68)	76	77	PG	Tc99m	75,50	-	P	-	-	40
Klapdor, 2015 (14)	38	40	PP	Tc99m	65,90	26,50	R	-	-	10,00
Rob, 2014 (69)	225	255	PP	Tc99m+Bd	66,40	-	P	-	-	-
Leitao, 2014 (70)	19	22	PG	ICG	-	-	P	1,25	20	-
	14	17	PG	Tc99m	-	-	P	1,25	20	-
	20	22	PG	Tc99m+ICG	-	-	P	1,25	20	-
Cintra, 2014 (71)	28	31	PP	Tc99m+Bd	-	-	P	-	-	-

Carrilho Vaz, 2014 (72)	177	190	PP	Tc99m	70,00	-	R	-	-	60
Boogerd, 2014 (73)	9	12	PP	ICG	-	-	P	0,6	-	-
	12	12	PP	Tc99m+ICG	-	-	P	0,12	-	-
Robison, 2014 (74)	103	111	PG	Tc99m+Bd	66,90	-	P	-	-	-
	95	111	PG	Tc99m	66,90	-	P	-	-	-
	75	111	PG	Bd	66,90	-	P	-	-	-
	63	69	PP	Tc99m+Bd	66,90	-	P	-	-	-
Nieves Maldonado, 2013 (75)	21	21	PP	Tc99m	-	-	R	-	-	111
Boran, 2013 (76)	24	24	PG	Tc99m	62,20	-	P	-	-	-
	18	18	PG	Tc99m+Bd	62,20	-	P	-	-	-
Mathéron, 2013 (77)	25	27	PG	Tc99m	66,00	25,30	P	-	-	87
	24	27	PG	ICG	66,00	25,30	P	-	-	-
	16	23	PG	Bd	66,00	25,30	P	-	-	-
Woelber, 2013 (78)	106	106	PP	Tc99m	-	-	R	-	-	85
Levenback, 2012 (31)	418	452	PP	Tc99m+Bd	-	-	P	-	-	-

	354	452	PP	Bd	-	-	P	-	-	-
	318	452	PP	Tc99m	-	-	P	-	-	-
Hutteman, 2012 (79)	9	9	PP	Tc99m	50,00	27,00	P	-	-	80
	9	9	PP	ICG	50,00	27,00	P	-	-	-
	8	9	PP	Bd	50,00	27,00	P	-	-	-
Brammen, 2012 (80)	94	102	PP	Tc99m	-	-	R	-	-	-
Bossé, 2012 (81)	107	108	PP	Tc99m+Bd	-	-	R	-	-	-
García-Iglesias, 2012 (82)	15	15	PP	Tc99m	76,00	-	R	-	-	90
	61	61	PP	Tc99m+Bd	76,00	-	R	-	-	90
Sawicki, 2011 (83)	31	39	PG	Bd	-	-	P	-	-	-
	16	18	PG	Tc99m	-	-	P	-	-	-
Klar, 2011 (84)	12	16	PP	Tc99m	65,60	-	P	-	-	10
Devaja, 2011 (85)	59	60	PP	Tc99m	63,00	-	P	-	-	40
	56	60	PP	Bd	63,00	-	P	-	-	-
Crane, 2011 (86)	16	16	PG	Tc99m	67,50	26,50	P	-	-	100
	15	16	PG	ICG	67,50	26,50	P	0,5	-	-

	13	16	PG	Bd	67,50	26,50	P	-	-	-
Akrivos, 2011 (87)	52	64	PG	Tc99m+Bd	69,10	-	P	-	-	-
Ennik, 2011 (88)	2	3	PG	Bd	-	-	R	-	-	-
	35	48	PG	Tc99m	-	-	R	-	-	-
	42	48	PG	Tc99m+Bd	-	-	R	-	-	-
	1	2	PP	Bd	-	-	R	-	-	-
	30	33	PP	Tc99m	-	-	R	-	-	-
	30	30	PP	Tc99m+Bd	-	-	R	-	-	-
Radziszewski, 2010 (33)	106	107	PG	Tc99m	68,00	-	P	-	-	-
	82	108	PG	Bd	68,00	-	P	-	-	-
Crosbie, 2010 (89)	41	45	PG	Tc99m+Bd	67,00	-	P	-	-	40
	40	45	PG	Tc99m	67,00	-	P	-	-	40
	38	45	PG	Bd	67,00	-	P	-	-	40
Lindell, 2010 (90)	94	126	PG	Tc99m+Bd	71,20	-	R	-	-	40,00
Levenback, 2009 (27)	306	318	PP	Tc99m+Bd	66,90	-	R	-	-	-
	67	85	PP	Bd	66,90	-	R	-	-	-

Achimas-Cadariu, 2009 (91)	30	32	PP	Tc99m+Bd	66,00	-	R	-	-	-
Camara, 2009 (92)	13	17	PP	Tc99m	-	-	P	-	-	-
	9	17	PP	Bd	-	-	P	-	-	-
	15	17	PP	Tc99m+Bd	-	-	P	-	-	-
Garcia, 2009 (93)	8	9	PP	Tc99m+Bd	61,30	-	R	-	-	-
Johann, 2008 (94)	37	39	PP	Tc99m+Bd	-	-	P	-	-	60
Rob, 2007 (95)	62	64	PG	Tc99m+Bd	69,80	-	P	-	-	15
	12	22	PG	Bd	69,80	-	P	-	-	-
Hauspy, 2007 (96)	58	68	PG	Tc99m+Bd	65,00	-	P	-	-	-
Vidal-Sicart, 2007 (97)	49	50	PP	Tc99m	75,00	-	P	-	-	148
	40	50	PP	Bd	75,00	-	P	-	-	-
Nyberg, 2007 (98)	45	47	PG	Bd	76,00	-	R	-	-	-
	37	40	PG	Tc99m	76,00	-	R	-	-	-
Martinez-Palonez, 2006 (99)	27	28	PP	Tc99m+Bd	70,70	-	P	-	-	-
Wydra, 2005 (100)	12	17	PG	Bd	66,00	-	P	-	-	-
	10	12	PG	Tc99m	66,00	-	P	-	-	52,5

Merisio, 2005 (36)	22	32	PG	Tc99m	75,00	-	P	-	-	11
Louis-Sylvestre, 2005 (35)	21	34	PG	Tc99m	62,40	-	P	-	-	30
	13	28	PG	Bd	62,40	-	P	-	-	-
Basta, 2005 (101)	38	39	PP	Tc99m	-	-	P	-	-	-
	32	39	PP	Bd	-	-	P	-	-	-
Carcopino, 2005 (102)	18	19	PG	Tc99m+Bd	-	-	R	-	-	-
	14	15	PP	Tc99m+Bd	-	-	R	-	-	-
Hakam, 2004 (103)	14	14	PP	Tc99m	59,00	-	R	-	-	-
Van den Eynden, 2003 (104)	27	32	PP	Tc99m+Bd	-	-	P	-	-	-
Moore, 2002 (37)	31	31	PG	Tc99m	79,00	-	P	-	-	-
	19	31	PG	Bd	79,00	-	P	-	-	-
Hartenbach, 2002 (34)	9	10	PP	Tc99m	66,50	-	P	-	-	-
	7	10	PP	Bd	66,50	-	P	-	-	-
Zámbó, 2002 (105)	12	14	PG	Tc99m	57,70	-	P	-	-	100
Molpus, 2001 (106)	10	11	PP	Tc99m	-	-	P	-	-	-

	10	11	PP	Bd	-	-	P	-	-	-
Sliutz, 2001 (107)	26	26	PP	Tc99m	63,80	-	P	-	-	15
	3	8	PP	Bd	63,80	-	P	-	-	-
Tavares, 2001 (38)	15	15	PP	Tc99m	-	-	P	-	-	64,5
Levenback, 2001 (25)	57	76	PG	Bd	58,00	-	P	-	-	-
Terada, 2000 (108)	9	9	PP	Tc99m+Bd	69,00	-	P	-	-	-
Sideri, 2000 (109)	77	77	PG	Tc99m	-	-	P	-	-	22
de Hullu, 2000 (110)	95	107	PG	Tc99m+Bd	69,00	-	P	-	-	60
De Cicco, 1999 (111)	37	37	PP	Tc99m	-	-	P	-	-	15
Echt, 1999 (112)	13	23	PG	Bd	-	-	P	-	-	-
Ansink, 1999 (32)	52	93	PG	Bd	70,00	-	P	-	-	-
Bowles, 1999 (113)	6	6	PP	Tc99m	-	-	P	-	-	15
Rodier, 1999 (114)	7	7	PP	Tc99m	65,00	-	P	-	-	14,8
	4	6	PP	Bd	65,00	-	P	-	-	-
DeCesare, 1997 (115)	10	10	PP	Tc99m	-	-	P	-	-	15

de Hullu, 1997 (11)	18	18	PG	Tc99m	68,00	-	P	-	-	60,00
	10	18	PG	Bd	68,00	-	P	-	-	60,00

Table 1. Basic characteristics of the included studies. PP= Per Patient, PG= Per Groin, PS= Per SLN. Age and BMI are mean scores. Study design: P=Prospective; R=Retrospective; RCT=Randomized Controlled Trial. Activities are in MBq. Concentrations are in ml/mg. Volumes are in ml.

4.2.3 Combined detection rates

A detailed quantitative synthesis was carried out to estimate the overall DR associated with SLN detection techniques across all included studies. The pooled per-patient DR was calculated at 92%, with a 95% confidence interval (CI) of [89%; 94%]. Similarly, the aggregated per-groin DR was determined to be 84%, with a 95% CI of [80%; 87%]. These findings represent the cumulative diagnostic performance of the evaluated methods and form the basis for subsequent comparative analyses.

4.2.4 Two-level analysis

4.2.4.1 Per-patient detection rates

Blue dye

An analysis of data from fourteen studies (27, 31, 34, 56, 64, 79, 85, 88, 92, 97, 101, 106, 107, 114), including a total of 836 patients, demonstrated a per-patient detection rate of 82% for blue dye. The corresponding 95% confidence interval was [72%; 89%], and heterogeneity across the studies was moderate, with I^2 = 60% [28%; 78%] (Figure 2/A).

Tc99m

A total of thirty studies (14, 16, 21, 31, 34, 38, 42, 43, 50, 56, 64, 72, 75, 78-80, 82, 84, 85, 88, 92, 97, 101, 103, 106, 107, 111, 113-115), comprising 1,532 patients, evaluated the per-patient DR of technetium-99m, which was found to be 98%, with a 95% CI of [94%; 99%]. Between-study heterogeneity was moderate to substantial, with an I^2 value of 67% [51%; 77%] (Figure 2/B).

ICG

The performance of ICG was assessed in six studies (50, 54, 59, 67, 73, 79), encompassing 124 patients. The pooled per-patient DR was 86%, with a 95% CI of [76%; 92%]. Heterogeneity in this group was negligible, with an I^2 of 0% [0%; 75%] (Figure 2/C).

SPIO

Three studies (21, 42, 43), including a total of 50 patients, analyzed SLN detection using SPIO. The pooled per-patient DR was 100%, though the 95% CI was wide, ranging from

[0%; 100%], due to the small sample size. Reported heterogeneity was minimal, with I^2 = 0% [0%; 90%] (Figure 2/D).

Tc99m combined with blue dye

A subgroup of twenty-one studies(27, 31, 39, 51, 58, 61, 65, 69, 71, 74, 81, 82, 88, 91-94, 99, 102, 104, 108), covering 1,933 patients, reported outcomes for the combined use of Tc99m and blue dye. The pooled per-patient DR was 94%, with a 95% CI of [91%; 96%], and I^2 was 52% [21%; 71%], indicating moderate heterogeneity (Figure 2/E).

Tc99m combined with ICG

In five studies (39, 53, 54, 66, 73), comprising 162 patients, the combination of Tc99m with ICG was assessed. The results showed a high pooled per-patient DR of 98%, with a 95% CI of [91%; 99%]. No notable heterogeneity was detected, with an I^2 value of 0% [0%; 79%] (Figure 2/F).

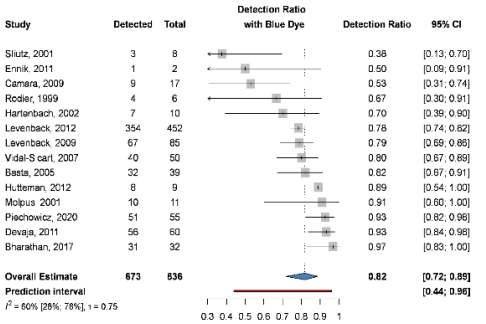


Figure 2/A. Per-Patient DR of Blue Dye single level forest plot.

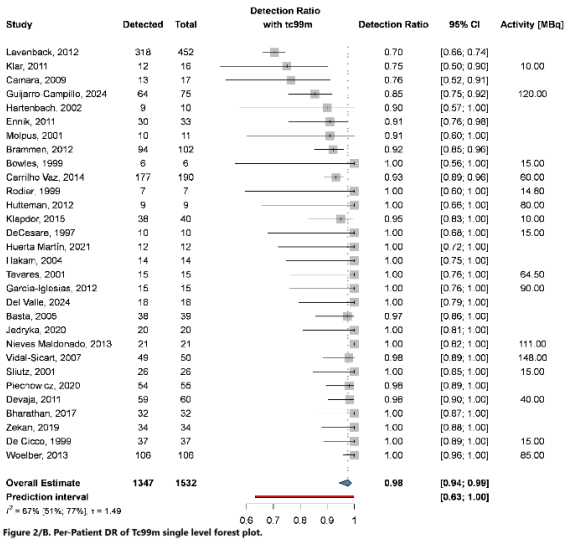


Figure 2/B. Per-Patient DR of Tc99m single level forest plot.

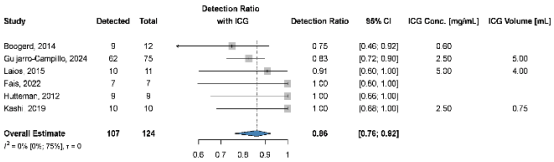


Figure 2/C. Per-Patient DR of ICG single level forest plot.

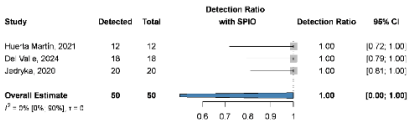


Figure 2/D. Per-Patient DR of SPIO single level forest plot.

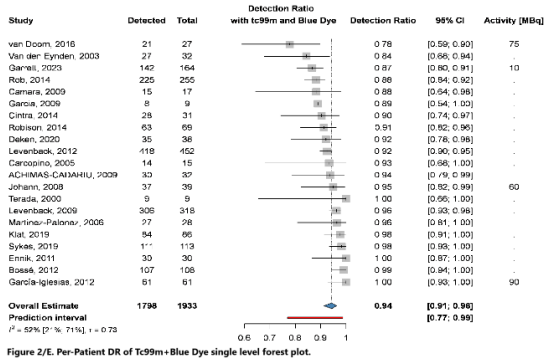


Figure 2/E. Per-Patient DR of Tc99m+Blue Dye single level forest plot.

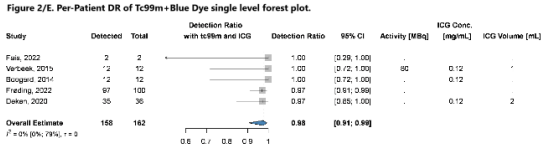


Figure 2/F. Per-Patient DR of Tc99m+ICG single level forest plot.

2. Figure Two-level, per-patient forest plots of the detection rates of the assessed methods.

4.2.4.2 Per-groin detection rates

Blue dye

An analysis of twenty-one studies (11, 13, 25, 32, 33, 35, 37, 40, 41, 60, 63, 74, 77, 83, 86, 88, 89, 95, 98, 100, 112), encompassing a total of 853 groins, revealed a per-groin detection rate of 69% for blue dye. The 95% confidence interval was [62%; 76%], with a moderate level of between-study heterogeneity observed (I^2 = 62% [39%; 76%]) (Figure 3/A).

Tc99m

The per-groin detection rate of Tc99m was evaluated across twenty-six studies (11-13, 15, 33, 35-37, 40, 41, 55, 60, 63, 68, 70, 74, 76, 77, 83, 86, 88, 89, 98, 100, 105, 109), covering 1,190 groins. The pooled detection rate was found to be 93%, with a 95% CI of [88%; 96%]. Moderate heterogeneity was present among the studies (I^2 = 58% [35%; 73%]) (Figure 3/B).

ICG

Data from ten studies (13, 15, 40, 41, 52, 60, 63, 70, 77, 86), involving 445 groins, indicated a per-groin detection rate of 90% for ICG. The 95% CI ranged from [83%; 94%], and heterogeneity across these studies was minimal (I^2 = 0% [0%; 62%]) (Figure 3/C).

SPIO

Due to the limited availability of data, a reliable estimation of the per-groin detection rate for SPIO could not be performed. The small number of studies reporting this outcome did not allow for meaningful statistical synthesis.

Tc99m combined with blue dye

A subgroup of fifteen studies (13, 52, 60, 62, 65, 74, 76, 87-90, 95, 96, 102, 110), including 1,355 groins, evaluated the combined use of Tc99m with blue dye. This combination yielded a pooled per-groin detection rate of 88%, with a 95% CI of [83%;

92%]. Considerable heterogeneity was observed in this group (I^2 = 84% [76%; 90%]) (Figure 3/D).

Tc99m combined with ICG

The combination of Tc99m and ICG was assessed in seven studies (13, 40, 41, 52, 57, 60, 70), encompassing 414 groins. The pooled per-groin detection rate was 95%, with a 95% CI of [87%; 98%]. Heterogeneity was low to moderate in this group (I^2 = 23% [0%; 66%]) (Figure 3/E).

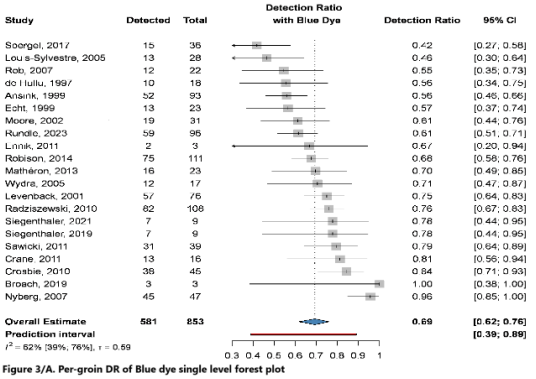


Figure 3/A. Per-groin DR of Blue dye single level forest plot

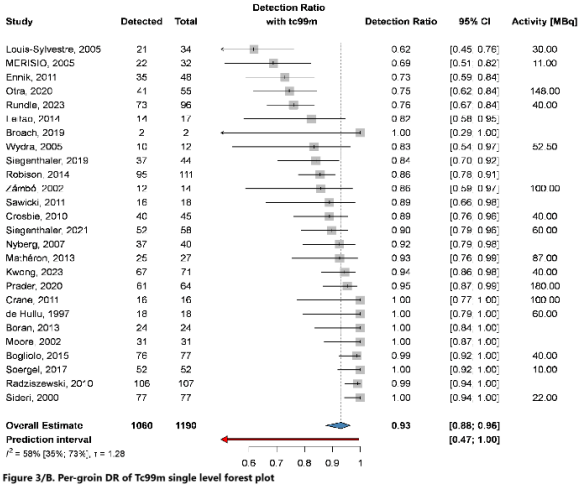


Figure 3/B. Per-groin DR of Tc99m single level forest plot

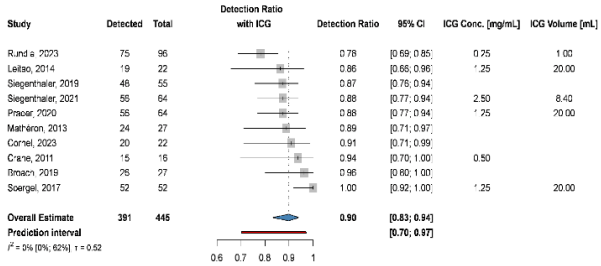


Figure 3/C. Per-groin DR of ICG single level forest plot

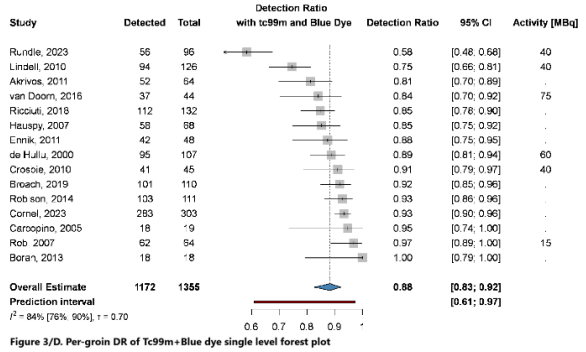


Figure 3/D. Per-groin DR of Tc99m+Blue dye single level forest plot

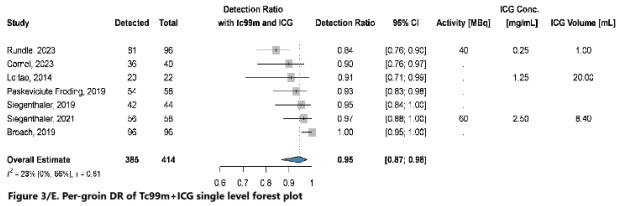


Figure 3/E. Per-groin DR of Tc99m+ICG single level forest plot

3. Figure Two-level, per-groin forest plots of the detection rates of the assessed methods.

4.2.5 Three-level analysis

4.2.5.1Per-patient detection rates

Blue Dye

A total of fourteen studies (27, 31, 34, 56, 64, 79, 85, 88, 92, 97, 101, 106, 107, 114), which together included 836 patients, reported on the performance of blue dye for SLN detection on a per-patient basis. The combined detection rate across these studies was 78%, with a 95% confidence interval of [69%; 85%] (Figure 4/A).

Tc99m

In thirty studies (14, 16, 21, 31, 34, 38, 42, 43, 50, 56, 64, 72, 75, 78-80, 82, 84, 85, 88, 91, 92, 97, 101, 103, 106, 107, 111, 113-115), encompassing 1,532 patients, Tc99m was evaluated for SLN identification. The pooled per-patient detection rate was 93%, with a 95% CI of [90%; 95%] (Figure 4/D).

ICG

The use of ICG was analysed in six studies (50, 54, 59, 67, 73, 79), involving 124 patients. These yielded a per-patient detection rate of 88%, with the 95% confidence interval spanning [76%; 95%] (Figure 4/B).

SPIO

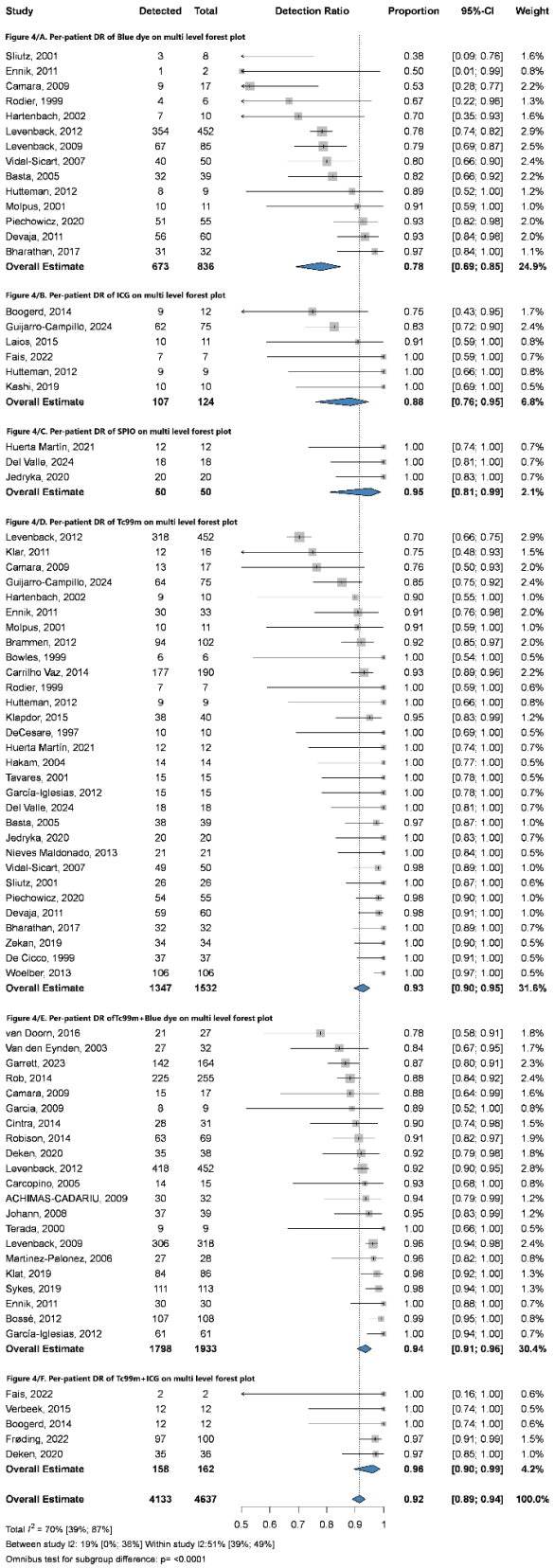
In three studies (21, 42, 43), which included a combined total of 50 patients, SPIO was assessed. The pooled analysis demonstrated a per-patient detection rate of 95%, with a 95% CI of [81%; 99%] (Figure 4/C).

Tc99m combined with blue dye

The combination of Tc99m and blue dye was examined in twenty-one studies (27, 31, 39, 51, 58, 61, 65, 69, 71, 74, 81, 82, 88, 91-94, 99, 102, 104, 108), comprising a total of 1,933 patients. This dual-tracer approach resulted in a per-patient detection rate of 94%, with a 95% CI of [91%; 96%] (Figure 4/E).

Tc99m combined with ICG

Five studies (39, 53, 54, 66, 73), which collectively enrolled 162 patients, evaluated the combination of Tc99m and ICG. The per-patient detection rate for this combination was 96%, with the 95% CI ranging from [90%; 99%] (Figure 4/F).


Study
Detected
Total
Detection Ratio
Proportion
95%-CI
Weight
Figure 4/A. Per-patient DR of Blue dye on multi level forest plot
Sliutz, 2001 3 8 0.38 [0.09; 0.76] 1.6%
Ennik, 2011 1 2 0.50 [0.01; 0.99] 0.8%
Camara, 2009 9 17 0.53 [0.28; 0.77] 2.2%
Rodier, 1999 4 6 0.67 [0.22; 0.96] 1.3%
Hartenbach, 2002 7 10 0.70 [0.35; 0.93] 1.6%
Levenback, 2012 354 452 0.78 [0.74; 0.82] 2.9%
Levenback, 2009 67 85 0.79 [0.69; 0.87] 2.5%
Vidal-Sicart, 2007 40 50 0.80 [0.66; 0.90] 2.4%
Basta, 2005 32 39 0.82 [0.66; 0.92] 2.2%
Hutteman, 2012 8 9 0.89 [0.52; 1.00] 1.2%
Molpus, 2001 10 11 0.91 [0.59; 1.00] 1.0%
Piechowicz, 2020 51 55 0.93 [0.82; 0.98] 2.0%
Devaja, 2011 56 60 0.93 [0.84; 0.98] 2.0%
Bharathan, 2017 31 32 0.97 [0.84; 1.00] 1.1%
Overall Estimate 673 836 0.78 [0.69; 0.85] 24.9%
Figure 4/B. Per-patient DR of ICG on multi level forest plot
Boogerd, 2014 9 12 0.75 [0.43; 0.95] 1.7%
Guijarro-Campillo, 2024 62 75 0.83 [0.72; 0.90] 2.4%
Laios, 2015 10 11 0.91 [0.59; 1.00] 0.8%
Fais, 2022 7 7 1.00 [0.59; 1.00] 0.7%
Hutteman, 2012 9 9 1.00 [0.66; 1.00] 0.8%
Keshi, 2019 10 10 1.00 [0.69; 1.00] 0.5%
Overall Estimate 107 124 0.88 [0.76; 0.95] 6.8%
Figure 4/C. Per-patient DR of SPIO on multi level forest plot
Huerta Martín, 2021 12 12 1.00 [0.74; 1.00] 0.7%
Del Valle, 2024 18 18 1.00 [0.81; 1.00] 0.7%
Jedryka, 2020 20 20 1.00 [0.83; 1.00] 0.7%
Overall Estimate 50 50 0.95 [0.81; 0.99] 2.1%
Figure 4/D. Per-patient DR of Tc99m on multi level forest plot
Levenback, 2012 318 452 0.70 [0.66; 0.75] 2.9%
Klar, 2011 12 16 0.75 [0.48; 0.93] 1.5%
Camara, 2009 13 17 0.76 [0.50; 0.93] 2.0%
Guijarro-Campillo, 2024 64 75 0.85 [0.75; 0.92] 2.4%
Hartenbach, 2002 9 10 0.90 [0.55; 1.00] 1.0%
Ennik, 2011 30 33 0.91 [0.76; 0.98] 2.0%
Molpus, 2001 10 11 0.91 [0.59; 1.00] 1.0%
Brammen, 2012 94 102 0.92 [0.85; 0.97] 2.0%
Bowles, 1999 6 6 1.00 [0.54; 1.00] 0.5%
Carrilho Vaz, 2014 177 190 0.93 [0.89; 0.96] 2.2%
Rodier, 1999 7 7 1.00 [0.59; 1.00] 0.6%
Hutteman, 2012 9 9 1.00 [0.66; 1.00] 0.8%
Klapdor, 2015 38 40 0.95 [0.83; 0.99] 1.2%
DeCesare, 1997 10 10 1.00 [0.69; 1.00] 0.5%
Huerta Martín, 2021 12 12 1.00 [0.74; 1.00] 0.7%
Hakam, 2004 14 14 1.00 [0.77; 1.00] 0.5%
Tavares, 2001 15 15 1.00 [0.78; 1.00] 0.5%
García-Iglesias, 2012 15 15 1.00 [0.78; 1.00] 0.7%
Del Valle, 2024 18 18 1.00 [0.81; 1.00] 0.7%
Basta, 2005 38 39 0.97 [0.87; 1.00] 1.0%
Jedryka, 2020 20 20 1.00 [0.83; 1.00] 0.7%
Nieves Maldonado, 2013 21 21 1.00 [0.84; 1.00] 0.5%
Vidal-Sicart, 2007 49 50 0.98 [0.89; 1.00] 1.0%
Sliutz, 2001 26 26 1.00 [0.87; 1.00] 0.6%
Piechowicz, 2020 54 55 0.98 [0.90; 1.00] 1.0%
Devaja, 2011 59 60 0.98 [0.91; 1.00] 1.0%
Bharathan, 2017 32 32 1.00 [0.89; 1.00] 0.7%
Zekan, 2019 34 34 1.00 [0.90; 1.00] 0.5%
De Cicco, 1999 37 37 1.00 [0.91; 1.00] 0.5%
Woelber, 2013 106 106 1.00 [0.97; 1.00] 0.5%
Overall Estimate 1347 1532 0.93 [0.90; 0.95] 31.6%
Figure 4/E. Per-patient DR of Tc99m+Blue dye on multi level forest plot
van Doorn, 2016 21 27 0.78 [0.58; 0.91] 1.8%
Van den Eynden, 2003 27 32 0.84 [0.67; 0.95] 1.7%
Garrett, 2023 142 164 0.87 [0.80; 0.91] 2.3%
Rob, 2014 225 255 0.88 [0.84; 0.92] 2.4%
Camara, 2009 15 17 0.88 [0.64; 0.99] 1.6%
Garcia, 2009 8 9 0.89 [0.52; 1.00] 0.8%
Cintra, 2014 28 31 0.90 [0.74; 0.98] 1.5%
Robison, 2014 63 69 0.91 [0.82; 0.97] 1.9%
Deken, 2020 35 38 0.92 [0.79; 0.98] 1.8%
Levenback, 2012 418 452 0.92 [0.90; 0.95] 2.8%
Carcopino, 2005 14 15 0.93 [0.68; 1.00] 0.8%
ACHIMAS-CADARIU, 2009 30 32 0.94 [0.79; 0.99] 1.2%
Johann, 2008 37 39 0.95 [0.83; 0.99] 1.2%
Terada, 2000 9 9 1.00 [0.66; 1.00] 0.5%
Levenback, 2009 306 318 0.96 [0.94; 0.98] 2.4%
Martinez-Palonez, 2006 27 28 0.96 [0.82; 1.00] 0.8%
Klat, 2019 84 86 0.98 [0.92; 1.00] 1.3%
Sykes, 2019 111 113 0.98 [0.94; 1.00] 1.3%
Ennik, 2011 30 30 1.00 [0.88; 1.00] 0.7%
Bossé, 2012 107 108 0.99 [0.95; 1.00] 0.8%
García-Iglesias, 2012 61 61 1.00 [0.94; 1.00] 0.7%
Overall Estimate 1798 1933 0.94 [0.91; 0.96] 30.4%
Figure 4/F. Per-patient DR of Tc99m+ICG on multi level forest plot
Fais, 2022 2 2 1.00 [0.16; 1.00] 0.6%
Verbeek, 2015 12 12 1.00 [0.74; 1.00] 0.5%
Boogerd, 2014 12 12 1.00 [0.74; 1.00] 0.6%
Frøding, 2022 97 100 0.97 [0.91; 0.99] 1.5%
Deken, 2020 35 36 0.97 [0.85; 1.00] 1.0%
Overall Estimate 158 162 0.96 [0.90; 0.99] 4.2%
Overall Estimate 4133 4637 0.92 [0.89; 0.94] 100.0%
0.5 0.6 0.7 0.8 0.9 1
Total I^2 = 70% [39%; 87%]
Between study I2: 19% [0%; 38%] Within study I2:51% [39%; 49%]
Omnibus test for subgroup difference: p= <0.0001

4. Figure Three-level, per-patient forest plots of the detection rates of the assessed methods.

4.2.5.2 Per-groin detection rates

Blue dye

An evaluation of twenty-one studies (11, 13, 25, 32, 33, 35, 37, 40, 41, 60, 63, 74, 77, 83, 86, 88, 89, 95, 98, 100, 112), encompassing 853 groins, reported a pooled per-groin detection rate of 66% for blue dye. The estimated 95% confidence interval was [58%; 73%], indicating moderate performance for this tracer when used independently (Figure 5/A).

Tc99m

[15–17, 19, 37, 39–41, 44, 45, 55, 60, 63, 68, 70, 74, 76, 77, 83, 86, 88, 89, 98, 100, 105, 109],

Across twenty-six studies (11-13, 15, 33, 35-37, 40, 41, 55, 60, 63, 68, 70, 74, 76, 77, 83, 86, 88, 89, 98, 100, 105, 109) which collectively examined 1,190 groins, the per-groin detection rate for Tc99m was found to be 87%, with a 95% CI ranging from [82%; 90%] (Figure 5/C).

ICG

The tracer ICG was assessed in ten studies (13, 15, 40, 41, 52, 60, 63, 70, 77, 86), involving 445 groins. The resulting per-groin detection rate was 87%, with a 95% CI of [81%; 92%], demonstrating a comparable performance to Tc99m in this dataset (Figure 5/B).

SPIO

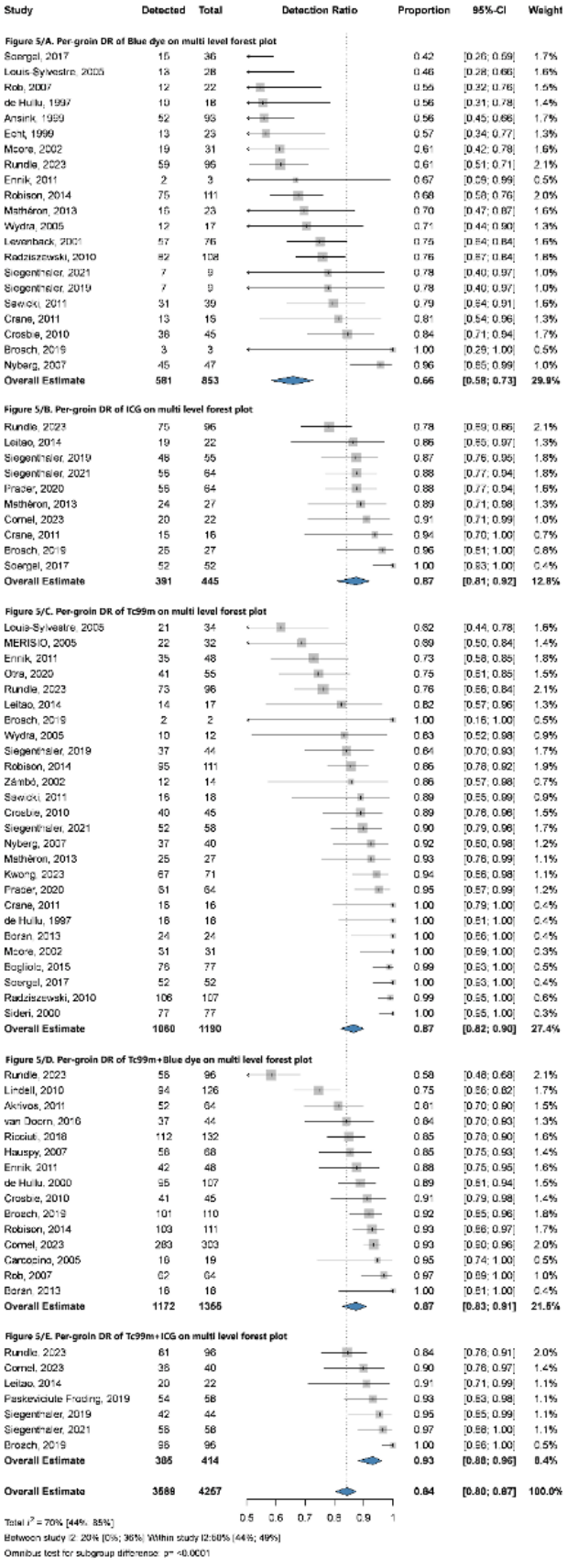
Due to the small number of available studies examining this tracer, a pooled per-groin detection rate for SPIO could not be established. The data were insufficient to permit statistical aggregation or meaningful inference.

Tc99m combined with blue dye

Fifteen studies (13, 52, 60, 62, 65, 74, 76, 87-90, 95, 96, 102, 110), comprising 1,355 groins, evaluated the combination of Tc99m and blue dye. The combined per-groin detection rate was 87%, with the 95% CI calculated at [83%; 91%] (Figure 5/D).

Tc99m combined with ICG

A total of seven studies (13, 40, 41, 52, 57, 60, 70), including 414 groins, assessed the effectiveness of the Tc99m and ICG combination. This dual-tracer method achieved a per-groin detection rate of 93%, with a 95% CI of [88%; 96%], indicating a high level of diagnostic reliability (Figure 5/E).


Study
Detected
Total
Detection Ratio
Proportion
95%-CI
Weight
Figure 5/A. Per-groin DR of Blue dye on multi level forest plot
Soergel, 2017 15 36 0.42 [0.26; 0.59] 1.7%
Louis-Sylvestre, 2005 13 28 0.46 [0.28; 0.66] 1.6%
Rob, 2007 12 22 0.55 [0.32; 0.76] 1.5%
de Hullu, 1997 10 18 0.56 [0.31; 0.78] 1.4%
Ansink, 1999 52 93 0.56 [0.45; 0.66] 1.7%
Echt, 1999 13 23 0.57 [0.34; 0.77] 1.3%
Moore, 2002 19 31 0.61 [0.42; 0.78] 1.6%
Rundle, 2023 59 96 0.61 [0.51; 0.71] 2.1%
Ennik, 2011 2 3 0.67 [0.09; 0.99] 0.5%
Robison, 2014 75 111 0.68 [0.58; 0.76] 2.0%
Matthéron, 2013 16 23 0.70 [0.47; 0.87] 1.6%
Wydra, 2005 12 17 0.71 [0.44; 0.90] 1.3%
Levenback, 2001 57 76 0.75 [0.64; 0.84] 1.6%
Radziszewski, 2010 82 108 0.76 [0.67; 0.84] 1.8%
Siegenthaler, 2021 7 9 0.78 [0.40; 0.97] 1.0%
Siegenthaler, 2019 7 9 0.78 [0.40; 0.97] 1.0%
Sawicki, 2011 31 39 0.79 [0.64; 0.91] 1.6%
Crane, 2011 13 15 0.87 [0.54; 0.96] 1.3%
Crosbie, 2010 38 45 0.84 [0.71; 0.94] 1.7%
Brosch, 2019 3 3 1.00 [0.29; 1.00] 0.5%
Nyberg, 2007 45 47 0.96 [0.85; 0.99] 1.0%
Overall Estimate 581 853 0.66 [0.58; 0.73] 29.9%
Figure 5/B. Per-groin DR of ICG on multi level forest plot
Rundle, 2023 75 96 0.78 [0.69; 0.86] 2.1%
Leitao, 2014 19 22 0.86 [0.65; 0.97] 1.3%
Siegenthaler, 2019 48 55 0.87 [0.76; 0.95] 1.8%
Siegenthaler, 2021 55 64 0.86 [0.77; 0.94] 1.8%
Fraser, 2020 55 64 0.86 [0.77; 0.94] 1.6%
Matthéron, 2013 24 27 0.89 [0.71; 0.98] 1.3%
Cornel, 2023 20 22 0.91 [0.71; 0.99] 1.0%
Crane, 2011 15 16 0.94 [0.70; 1.00] 0.7%
Brosch, 2019 25 27 0.96 [0.81; 1.00] 0.8%
Soergel, 2017 52 52 1.00 [0.93; 1.00] 0.4%
Overall Estimate 391 445 0.87 [0.81; 0.92] 12.8%
Figure 5/C. Per-groin DR of Tc99m on multi level forest plot
Louis-Sylvestre, 2005 21 34 0.62 [0.44; 0.78] 1.6%
MERISIO, 2005 22 32 0.69 [0.50; 0.84] 1.4%
Ennik, 2011 35 48 0.73 [0.58; 0.85] 1.8%
Ota, 2020 41 55 0.75 [0.61; 0.85] 1.5%
Rundle, 2023 73 96 0.76 [0.66; 0.84] 2.1%
Leitao, 2014 14 17 0.82 [0.57; 0.96] 1.3%
Brosch, 2019 2 2 1.00 [0.16; 1.00] 0.5%
Wydra, 2005 10 12 0.83 [0.52; 0.98] 0.9%
Siegenthaler, 2019 37 44 0.84 [0.70; 0.93] 1.7%
Robison, 2014 95 111 0.86 [0.78; 0.92] 1.9%
Zámbó, 2002 12 14 0.86 [0.57; 0.98] 0.7%
Sawicki, 2011 16 18 0.89 [0.65; 0.99] 0.9%
Crosbie, 2010 40 45 0.89 [0.76; 0.96] 1.5%
Siegenthaler, 2021 52 58 0.90 [0.79; 0.96] 1.7%
Nyberg, 2007 37 40 0.92 [0.80; 0.98] 1.2%
Matthéron, 2013 25 27 0.93 [0.76; 0.99] 1.1%
Kwong, 2023 67 71 0.94 [0.86; 0.98] 1.1%
Fraser, 2020 61 64 0.95 [0.87; 0.99] 1.2%
Crane, 2011 16 16 1.00 [0.79; 1.00] 0.4%
de Hullu, 1997 18 18 1.00 [0.81; 1.00] 0.4%
Borán, 2013 24 24 1.00 [0.86; 1.00] 0.4%
Moore, 2002 31 31 1.00 [0.89; 1.00] 0.3%
Baglioli, 2015 76 77 0.99 [0.93; 1.00] 0.5%
Soergel, 2017 52 52 1.00 [0.93; 1.00] 0.4%
Radziszewski, 2010 106 107 0.99 [0.95; 1.00] 0.6%
Sideri, 2009 77 77 1.00 [0.95; 1.00] 0.3%
Overall Estimate 1060 1190 0.87 [0.82; 0.90] 27.4%
Figure 5/D. Per-groin DR of Tc99m+Blue dye on multi level forest plot
Rundle, 2023 56 96 0.58 [0.48; 0.68] 2.1%
Lindell, 2010 94 126 0.75 [0.66; 0.82] 1.7%
Akrivos, 2011 52 64 0.81 [0.70; 0.90] 1.5%
van Doorn, 2016 37 44 0.84 [0.70; 0.93] 1.3%
Ricciuti, 2018 112 132 0.85 [0.78; 0.90] 1.6%
Hauspy, 2007 58 68 0.85 [0.75; 0.93] 1.4%
Ennik, 2011 42 48 0.88 [0.75; 0.95] 1.6%
de Hullu, 2000 95 107 0.89 [0.81; 0.94] 1.5%
Crosbie, 2010 41 45 0.91 [0.79; 0.98] 1.4%
Brosch, 2019 101 110 0.92 [0.85; 0.96] 1.8%
Robison, 2014 103 111 0.93 [0.86; 0.97] 1.7%
Cornel, 2023 283 303 0.93 [0.90; 0.96] 2.0%
Carcozino, 2005 18 19 0.95 [0.74; 1.00] 0.5%
Rob, 2007 62 64 0.97 [0.89; 1.00] 1.0%
Borán, 2013 18 18 1.00 [0.81; 1.00] 0.4%
Overall Estimate 1172 1365 0.87 [0.83; 0.91] 21.5%
Figure 5/E. Per-groin DR of Tc99m+ICG on multi level forest plot
Rundle, 2023 81 96 0.84 [0.76; 0.91] 2.0%
Cornel, 2023 38 40 0.90 [0.76; 0.97] 1.4%
Leitao, 2014 20 22 0.91 [0.71; 0.99] 1.1%
Paskeviciute Frading, 2019 54 58 0.93 [0.83; 0.98] 1.1%
Siegenthaler, 2019 42 44 0.95 [0.85; 0.99] 1.1%
Siegenthaler, 2021 58 58 0.97 [0.88; 1.00] 1.1%
Brosch, 2019 96 96 1.00 [0.96; 1.00] 0.5%
Overall Estimate 385 414 0.93 [0.89; 0.96] 8.4%
Overall Estimate 3589 4267 0.84 [0.80; 0.87] 100.0%
0.5 0.6 0.7 0.8 0.9 1
Total I^2 = 70% [44%; 85%]
Between study I2: 20% [0%; 36%] Within study I2:68% [44%; 49%]
Omnibus test for subgroup difference: p= <0.0001

5. Figure Three-level, per-groin forest plots of the detection rates of the assessed methods.

4.2.6 Risk of Bias Assessment and Evaluation of Publication Bias

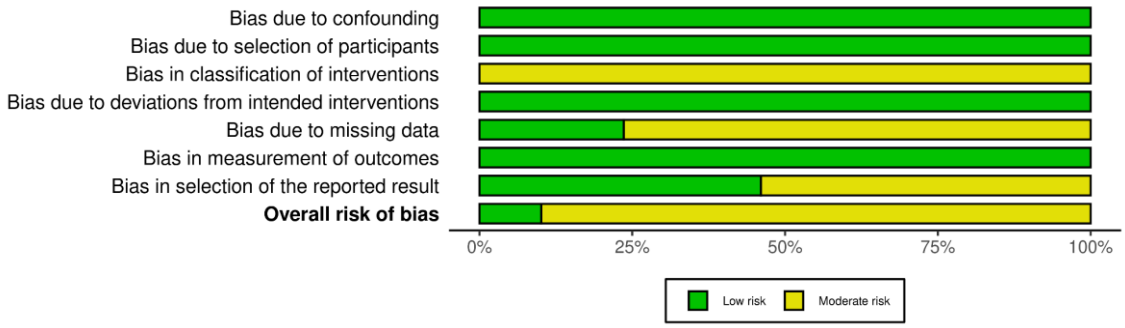
A critical component of any systematic review and meta-analysis is the rigorous evaluation of potential biases within the included studies. In the present analysis, the majority of the included studies were observational in design, which inherently introduces a moderate risk of bias due to limitations in randomization, blinding, and confounding control. However, it is important to note that a number of these studies demonstrated strong methodological rigor, including well-defined inclusion criteria, standardized outcome reporting, and consistent data collection procedures. As a result, several observational studies were ultimately assessed as having a low overall risk of bias, highlighting the heterogeneity in quality across the dataset.

To systematically assess methodological quality, the ROBINS-I tool was employed for all 86 observational studies. This validated tool evaluates risk across multiple domains, including bias due to confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of reported results. Each domain was rated individually, and then synthesized into an overall judgment of bias for each study. Studies were categorized as having a low, moderate, serious, or critical risk of bias based on the cumulative assessment across these dimensions.

For the RCTs included in the review, the RoB 2 tool was utilized. This instrument specifically accounts for the structured nature of RCTs and examines five key areas: bias arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of the reported result. The risk of bias judgments derived from this tool were similarly expressed as “low-risk,” “some concerns,” or “high-risk.”

All risk of bias evaluations were graphically visualized using the robvis tool, a software package designed to facilitate transparent presentation of quality assessments in systematic reviews. These visual summaries offer a clear and intuitive depiction of risk ratings across studies and domains, enabling readers to assess the overall strength of the

evidence base at a glance. The complete set of 115 risk of bias evaluations can be found in Figures 6 and 7.

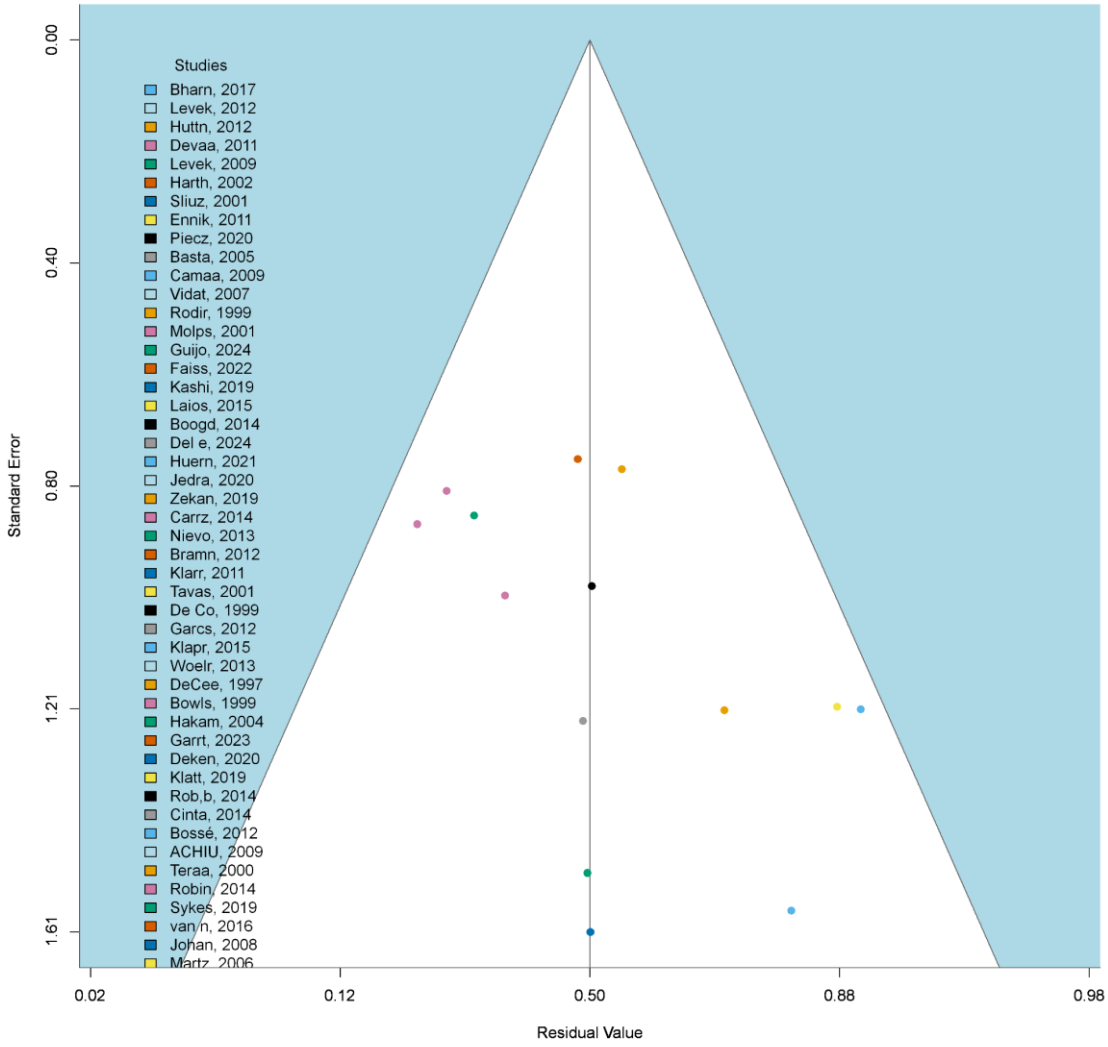


6. Figure Risk of bias chart. The ROBINS-I tool was used to evaluate the risk of bias of each study and to make the chart.

7. Figure The detailed risk of bias chart for the 2 involved RCTs. The chart was made using the Rob2 tool.

In addition to assessing study-level risk of bias, the potential for publication bias, a form of reporting bias where studies with positive or significant results are more likely to be published was explored. This was done through the construction of funnel plots, a widely used graphical method for evaluating asymmetry in the distribution of study effect sizes.

The results of these assessments are presented in Figures 8, providing additional context for interpreting the robustness of the pooled estimates derived from the meta-analysis.



8. Figure The funnel plot assesses the publication bias of the studies, regarding the per-groin DR.

4.2.7 Certainty of evidence assessment

To evaluate the overall confidence in the outcomes reported across the included studies, the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation)

methodology was applied. This structured and internationally recognized framework enables transparent assessment of evidence quality across multiple domains. Each pooled detection rate was independently appraised according to GRADE criteria, including risk of bias, inconsistency, indirectness, imprecision, and publication bias.

Following a comprehensive review, the certainty of evidence for DRs associated with each tracer modality: blue dye, Tc99m, ICG, SPIO, and their respective combinations was rated as high. This reflects a strong degree of confidence that the estimated detection rates are close to the true values and are unlikely to change with future research. The robustness of this evaluation was underpinned by the inclusion of a large number of studies with consistent findings, precise estimates, and generally low susceptibility to methodological flaws. Across all domains, no serious limitations were identified; each criterion was consistently rated as "not serious," indicating that downgrading of certainty was not warranted.

Particular attention was given to the clinical relevance of each tracer's contribution to SLN detection. The use of Tc99m, ICG, and their combinations was classified as providing critical information for surgical planning and clinical decision-making in the management of vulvar cancer. These tracers not only demonstrated superior detection rates but also supported intraoperative efficiency and accuracy. In contrast, blue dye as a standalone method, while still considered valuable, was assigned a slightly lower clinical importance, being rated as important rather than critical. This distinction reflects both its declining use in modern clinical settings and its lower performance metrics compared to newer or combined techniques.

Overall, the high-certainty ratings assigned through the GRADE approach reinforce the reliability and applicability of the findings presented in this review. These results offer a solid foundation for future guideline development and support evidence-based decision-making in sentinel lymph node detection strategies for vulvar cancer.

4.2.8 Reporting of Patient and Procedural Variables

Several of the included studies provided additional information on key demographic and procedural variables, including mean BMI, mean patient age, ICG concentration and

volume, and the activity levels of Tc99m used during sentinel lymph node procedures. While these data points are of clinical interest and may have potential relevance for stratified analyses, their heterogeneous nature, coupled with frequent incompleteness and inconsistency in reporting formats, prevented them from being statistically synthesized within the meta-analytic models.

In particular, variations in units, missing values, and lack of standardized reporting across studies limited the possibility of conducting subgroup or sensitivity analyses involving these variables. Despite these limitations, the available data have been extracted and are summarized to the extent possible in the baseline characteristics table to offer contextual insight into study populations and procedural protocols. The data assessed in this summary is presented in Table 1, allowing readers to assess the distribution and variability of these factors across the included studies, even though they were not quantitatively integrated into the main analysis.

4.3 Cervical Cancer During Pregnancy: A Multidisciplinary Approach to a Complex Oncological Case

This thesis also includes a clinically significant case that highlights the practical challenges of managing cervical cancer in pregnancy—a scenario where oncological and obstetric priorities intersect in a high-stakes clinical environment. The case is presented here as a complementary result to the broader analysis of sentinel lymph node detection methods and individualized treatment strategies in gynaecologic oncology.

4.3.1 Patient Background and Initial Diagnosis

A 32-year-old patient presented with a confirmed pregnancy in May 2024. Notably, a prior cytology in December 2023 had already revealed an ASC-H abnormality, with HPV testing positive for type 18 and methylation markers confirming oncogenic activity. Despite initially negative immunocytology (p16/Ki-67), a follow-up cytology at pregnancy confirmation indicated glandular epithelial neoplasia. Diagnostic loop conization was performed, and histopathological examination revealed a grade 3 HPV-associated squamous cell carcinoma, without lymphovascular space invasion.

4.3.2 Imaging, Staging, and Surgical Lymph Node Evaluation

Pelvic MRI confirmed a 30 mm cervical lesion confined to the cervix without parametrial or nodal involvement. Despite the imaging findings, sentinel and pelvic lymph node status were surgically assessed due to the limited sensitivity of imaging during pregnancy. A robot-assisted sentinel lymph node biopsy and bilateral pelvic lymphadenectomy were performed at 16 weeks of gestation. Pathological analysis of 28 lymph nodes confirmed the absence of metastasis. The use of minimally invasive robotic surgery enabled safe access to the lymphatic basins early in gestation, underscoring the feasibility of SLN procedures in selected pregnant patients.

4.3.3 Neoadjuvant Chemotherapy and Disease Progression

Based on oncological board recommendations, neoadjuvant chemotherapy (paclitaxel 350 mg + carboplatin 600 mg every 3 weeks) was initiated following lymph node staging. Interim MRI after three cycles revealed tumour progression, with maximum tumour diameter increasing from 30 mm to 48 mm. Despite the absence of nodal or distant metastasis, the lack of therapeutic response necessitated a re-evaluation of management strategy.

4.3.4 Delivery and Radical Surgical Management

In response to tumour progression and considering foetal development, the patient underwent caesarean section at 29 weeks of gestation after administration of antenatal corticosteroids for foetal lung maturation. A simultaneous radical hysterectomy (type C1) was performed. The neonate, weighing 1280 grams, required NICU admission due to respiratory distress syndrome, managed successfully with non-invasive ventilation and surfactant therapy.

4.3.5 Pathological Findings

Final histopathological evaluation confirmed a high-grade, HPV-associated squamous cell carcinoma with mucinous differentiation, measuring 65 mm craniocaudally and 42 mm laterally. The tumour infiltrated the outer third of the cervical stroma but spared the parametrium, vaginal wall, and other adjacent structures. Lymphovascular invasion was identified in three foci, while all surgical margins and lymph nodes, including parametrial nodes, were free of malignancy.

4.3.6 Postoperative Course and Adjuvant Therapy

Given the high-grade features, depth of stromal invasion, and presence of LVSI, the patient was classified as intermediate risk. The institutional gynaecologic oncology board recommended adjuvant radio-chemotherapy, consisting of external beam radiotherapy (EBRT) in 25 fractions totalling in 50.4 Gy. No postoperative complications were reported, and spontaneous lactation did not occur, eliminating the need for suppression.

4.3.7 Clinical Relevance of the Case

The utility of SLN mapping and pelvic lymphadenectomy during pregnancy, facilitated by robotic-assisted minimally invasive surgery, proved essential in early staging and risk stratification without compromising gestational integrity at that stage. The challenge of tumour progression despite neoadjuvant chemotherapy, emphasizing the importance of close monitoring and multidisciplinary decision-making when managing aggressive cervical cancer in pregnant patients. The timing of delivery and coordinated surgical intervention, which enabled oncologic resection while optimizing neonatal outcomes, underscoring the need for collaboration between obstetricians, oncologists, neonatologists, and surgical teams. The implications for future management protocols, as this case illustrates the potential value of sentinel node biopsy in guiding treatment even in pregnancy, a topic typically underrepresented in prospective trials.

5 Discussion

The management of HPV-associated malignancies, particularly vulvar and cervical cancers, has undergone notable evolution in recent years, driven by advancements in diagnostic technologies and a deeper understanding of tumour biology. The three studies presented in this thesis collectively highlight a shared objective: optimizing patient outcomes while minimizing procedural morbidity, an especially vital consideration in both oncological and obstetric contexts.

The systematic review and meta-analysis on SLN detection techniques in vulvar cancer reaffirm the central role of SLN biopsy in accurate staging, especially in early-stage disease. By aggregating data from 88 studies and over 4,600 patients, the research demonstrates that novel tracers such as ICG and SPIO can achieve detection rates comparable to, or in the case of SPIO, possibly exceeding, the traditionally recommended combination of Tc99m and blue dye or ICG. Importantly, these alternatives offer logistical and clinical benefits: ICG facilitates intraoperative visualization, while SPIO circumvents the need for radioactive materials, making them particularly promising in radiation-restricted settings. These findings provide compelling evidence to reconsider current ESGO and NCCN recommendations and support the broader implementation of ICG or SPIO-based techniques.

The protocol paper complements this by providing a rigorous methodological framework for evaluating SLN detection strategies, ensuring transparency and reproducibility. It emphasizes not only the comparative efficacy of different techniques but also the necessity to account for patient-specific variables such as BMI, tumour size, and tracer dosing, factors that can influence detection success and should inform individualized treatment planning.

In contrast, the case report of cervical cancer during pregnancy illustrates the unique challenges of oncologic management within the delicate context of gestation. Despite the rarity of such cases, the growing prevalence of late maternal age necessitates a multidisciplinary approach that balances foetal viability with oncologic safety. The patient described in the report benefited from timely sentinel node evaluation via robotic-assisted lymphadenectomy and neoadjuvant chemotherapy, followed by preterm caesarean delivery and radical hysterectomy. This case highlights the pivotal role of

minimally invasive SLN techniques even during pregnancy, underlining their feasibility and importance in treatment planning.

Together, these studies underscore a paradigm shift toward more nuanced, patient-tailored oncologic care. Sentinel node biopsy, whether guided by Tc99m, ICG, or SPIO, emerges as a cornerstone of surgical staging in HPV-associated malignancies. Moreover, the personalized approach in pregnancy illustrates how technological advancements can be safely adapted to high-risk, complex scenarios. Moving forward, continued research into the comparative performance, accessibility, and cost-effectiveness of SLN detection methods is essential, especially to extend equitable care across diverse clinical environments.

6 Conclusions

This thesis explores key clinical and scientific questions in the management of gynaecologic malignancies, focusing on SLN detection techniques and their application in both standard and complex patient populations. The research addresses five core objectives, each contributing to a broader understanding of how diagnostic and surgical practices can be improved for personalized, evidence-based cancer care.

1. First, we conducted a comprehensive comparative analysis of SLN detection techniques in vulvar cancer. Our findings reveal that blue dye, while historically important, demonstrates limited reliability when used as a single agent due to its lower detection rate. Tc99m remains a robust and widely used tracer, but its dependence on nuclear medicine infrastructure presents practical challenges. In contrast, ICG achieves comparable detection efficacy with fewer logistical limitations and adverse effects, positioning it as a strong candidate for broader clinical adoption.
2. Second, we investigated the emerging role of SPIO as a novel tracer for SLN detection. Although current data suggest that SPIO may achieve detection rates on par with established methods, the limited number of studies and relatively small patient populations preclude definitive conclusions. We identify SPIO as a promising technology that warrants further prospective research, particularly in multicentre trials involving diverse populations. Its non-radioactive nature and flexibility of use may offer advantages in specific clinical settings.
3. Third, we directly compare ICG to guideline-recommended dual tracer methods, including Tc99m+BD and Tc99m+ICG. Our meta-analysis shows that ICG alone performs similarly in terms of detection rate, without statistically significant inferiority. This finding supports the consideration of ICG as a standalone alternative in selected cases, particularly when access to radiotracers is limited or contraindicated. These results contribute to ongoing efforts to refine SLN mapping protocols and inform future updates to clinical guidelines in gynaecologic oncology.
4. Fourth, we examined the unique challenges associated with managing cervical cancer during pregnancy. Our findings underscore the importance of a multidisciplinary approach, where oncologists, obstetricians, neonatologists, and surgical teams collaborate to develop individualized treatment strategies. Through an illustrative

case study, we demonstrate that early staging, using robot-assisted lymphadenectomy and SLN biopsy is both feasible and safe during pregnancy, and enables timely neoadjuvant treatment. Centralization of care in specialized centres is emphasized as essential for optimizing outcomes in this rare but high-risk clinical scenario.

5. Finally, we assessed the safety and feasibility of SLN detection and dissection in pregnant patients with cervical cancer. Our analysis highlights that gestational age is a key determinant of surgical approach, and that robotic assistance may offer improved precision and safety during minimally invasive lymphatic mapping. We propose that ICG is the most suitable tracer in this context due to its high detection rate, excellent visualization properties, and favourable safety profile. This work contributes to a growing body of evidence supporting SLN mapping as a valuable diagnostic tool in pregnancy-associated gynaecologic cancers.

7 Summary

Introduction

This dissertation investigates novel strategies in the diagnosis and management of HPV-related malignancies in gynaecological oncology. Despite advances in screening and vaccination, cervical and vulvar cancers pose significant clinical challenges, particularly during pregnancy. The thesis addresses two key areas: the comparative efficacy of SLN detection techniques in vulvar cancer and the multidisciplinary management of cervical cancer in pregnancy.

Methods

First, a systematic review and meta-analysis synthesized data from 88 studies (n=4,637) to evaluate SLN detection techniques in vulvar cancer. Random effects models and subgroup analyses were employed to compare the detection rates. Second, a retrospective case study analysed a 32-year-old pregnant patient treated for high-grade HPV-associated cervical cancer using minimally invasive surgery and neoadjuvant chemotherapy.

Results

In vulvar cancer, our meta-analysis found that ICG alone performs similarly as the guideline recommended combined methods. SPIO showed promising results but requires further validation due to limited data. The case study demonstrated the available treatment pathways and the feasibility and safety of robot-assisted SLN biopsy and tailored chemotherapy during pregnancy without compromising maternal or neonatal outcomes.

Conclusion

This thesis underscores the need for individualized, multidisciplinary approaches in managing HPV-associated malignancies. It advocates for integrating novel SLN detection agents, such as ICG and SPIO, into clinical practice to reduce surgical morbidity without compromising diagnostic accuracy. Moreover, it illustrates that effective oncologic treatment during pregnancy is feasible with careful coordination. The findings support updating current guidelines to reflect emerging evidence, particularly in underserved clinical scenarios like cancer during pregnancy or in settings without access to nuclear medicine.

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Publications not related to the thesis:

Vida, B., Keszthelyi, E., Tóth, Z., Lőczi, L., Sebők, B., Merkely, P., Lintner, B., Bánhidy, F., Keszthelyi, A., Várbíró, S., Tóth, R., & Keszthelyi, M. (2025). The Neutrophil-to-Lymphocyte Ratio (NLR) as A Potential Predictor in Conization Outcomes for Cervical Cancer. Cancers, 17(11), 1856. https://doi.org/10.3390/cancers17111856 IF: 4.5

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∑IF: 24,7

10. Acknowledgements

I would like to express my sincere gratitude to all my colleagues, mentors, and friends, without whose support and encouragement, this work would not have been possible.

First and foremost, I am deeply grateful to Dr. Márton Keszthelyi for his invaluable guidance, continuous support, and insightful advice throughout my PhD studies. His mentorship has greatly shaped both my research and my professional development.

I would also like to express my thanks to Dr. Richárd Tóth for his help, constructive feedback, and the knowledge he generously shared during our collaborations.

My sincere thanks go to Dr. Balázs Lintner for his essential contributions to our joint projects. His supervision, guidance, and dedication were instrumental to the success of this work.

I wish to thank Professor Szabolcs Várbíró for including our project in his research program, and Professor Nándor Ács for providing the opportunity to conduct our studies at his esteemed clinic.

Special thanks are due to the Science Management Working Group and the Doctoral School for their support in facilitating the completion of this dissertation.

I would also like to acknowledge all my colleagues who participated in and supported our research, including Dr. Lotti Keszthelyi, Dr. Dániel Sándor Veres, Dr. Zoltán Novák, and Dr. Lilla Madaras.

Finally, I owe my deepest gratitude to my family for their unwavering love, patience, and encouragement throughout my studies.