Review

The Evolution of Sentinel Node Biopsy in Urological Malignancy

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Abstract

Sentinel lymph node biopsy (SLNB) provides an accurate staging tool for a variety of malignancies including urological cancers. Initially introduced as a single procedure technique, SLNB has evolved into a dynamic multi-stage procedure that has an invaluable impact on the management of cancer patients. After a thorough literature search, this article summarizes the advancement of the SLNB procedure since its conception. The introduction of radioactive tracers and blue dye has resulted in a highly sensitive technique but one around which concerns persist. This paper updates existing material on the topic by examining the potential of near infra-red fluorescence optical imaging agents (NIRF) and anatomical fusion imaging as useful adjuncts to the currently practiced technique. SLNB has an established role in penile cancer with a well-documented improvement in morbidity and mortality rates. The presence of sentinel nodes in pelvic malignancy is controversial but papers have established that the technique is feasible for use in such cancers and that NIRF may have a role to play here in the future. SLNB currently has no place in the management of testicular or renal malignancy.

Keywords: Sentinel nodes; Lymph nodes; Penile cancer

Introduction

In recent years sentinel lymph node biopsy (SLNB) has revolutionized the management of patients with suspected regionally advanced malignancy. Widely used in both breast cancer and melanoma as well as urological malignancy, the technique is built around Halsted's theory which recognizes that cells from the primary tumor spread sequentially along the lymph chain becoming trapped in the first node and spreading further only once that node becomes overwhelmed (1). These first nodes are known as sentinel nodes (SNs) and were initially described in parotid malignancy by Gould in 1960 (2). Removal and pathological analysis of such nodes, allows clinicians to stage disease and identify patients in need of further regional or systemic treatment. It is preferred compared to more extensive surgery as it achieves lower morbidity rates relative to those seen in regional lymph node dissection (LND) (3).

The existence of SNs was previously confirmed and marked using lymphangiograms intra-operatively and now lymphangioscintograms preoperatively. However, dependence on these techniques alone meant that location of such nodes by the surgeon was still largely determined anatomically and did not allow for inter-patient variation (4). This changed in 1989 with the introduction of patent blue dye as a means of cutaneous lymph node mapping (5). Identification of SNs using blue dye mapping, with an injection at the site of the primary tumor, was first proposed for breast cancer in

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The abbreviations used: LN, lymph nodes; LNDs, lymph node dissections; MRI, magnetic resonance imaging; NIRF, near infra-red fluorescence optical imaging agents; SLNB, sentinel lymph node biopsy; SN, sentinel nodes; SPECT-CT, single photon emission computed tomography combined with CT; US, ultrasound.

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1994 and is now widely used in SLNB for a variety of malignancies (6).

The introduction of hand held gamma radiation probes intra-operatively in SLNB was reported as an alternative to blue dye mapping by a team at the University of Vermont Medical Centre. They went on to propose that this method had a number of advantages over its counterpart, namely that it can be used to confirm that the correct node has been biopsied as well as identifying the potential existence of remaining undissected SNs (7).

In its current form SLNB is not without limitations. Several papers have raised concerns about the high false negative rates, a recent paper citing a figure as high as 15% in penile cancer (8). It is anticipated that addition of newer techniques to dynamic SNLB will improve this and literature currently available explores a number of options.

Whilst not widely implemented, a role for a portable gamma camera was proposed as a potential alternative in centres where preoperative lymphoscintigraphy was not available. Trialled in breast and gynaecology malignancy, as well as head and neck cancers, studies have shown that it may be useful in visualizing and identifying nodes intra-operatively (9-10) even identifying nodes not seen preoperatively (11). It may also have a role in confirming removal of all radioactive nodes after a surgeon has completed the resection (12). Whether a defined role for the gamma camera becomes apparent in urological SLNB remains unclear but is unlikely given that studies have demonstrated the superiority of the conventional preoperative imaging in detecting SNs (13).

More promising however, is hybrid imaging using the concept of anatomical fusion. In 2006 a study in Sweden proposed the use of hybrid single photon emission computed tomography combined with CT (SPECT –CT) as an alternative to planar imaging to improve the SLNB technique in bladder cancer. They determined a significant improvement in the localization of SNs preoperatively, citing that preoperative lymphoscintigraphy using the hybrid technique identified 21 lymph nodes in five patients, compared to just two seen with conventional planar imaging (14). Such hybrid imaging has also been studied in penile and renal cancer with evidence that it is feasible for use in this role (15-16) as well as in gynaecological, breast and head and neck cancers (17-19).

Perhaps the most significant recent step in the evolution of sentinel node biopsy was the introduction of NIRF. NIRF provides a non radioactive, more penetrative, real time alternative to the tracers currently in use. It was studied in mice in 2003 (20) and in 2005, Melancon et al. demonstrated this to be a more effective method of identifying SNs in breast cancer, identifying all six superficial cervical nodes compared to T1 weighted MR which identified just four (21). In 2011 NIRF, in the form of indocyanine, was introduced to urological malignancy and used to identify lymphatic pathways in 14 patients with prostate cancer (22). Studies since then have shown that it can be used in a similar role for bladder cancer (23) but it was only earlier this year, after successfully identifying sentinel drainage in nine out of ten patients with bladder cancer and 38 of 50 patients with prostate cancer, that NIRF has been demonstrated as a feasible technique for aiding SLNB in robotically assisted procedures (24-25).

The concept of a hybrid tracer, combining the success of radioactive tracers and NIRF imaging was first suggested for prostate cancer in 2011 (26). In 2012, Brouwer et al. proposed indocyanine green-(99m)Tc-nanocolloid, a multimodal tracer as an replacement for blue dye in penile cancer. They not only demonstrated increased sensitivity, citing that it allowed visualisation of 96.8% of SNs compared to blue dye which stained just 55.7%, but that it could have a dual role as a suitable replacement for (99m)Tc-nanocolloid with which it has the same lymphatic drainage pattern (27-28). The concept of the hybrid tracer has yet to be widely implemented but there is support for its use in penile, prostate and breast cancer (29-30).

Whilst there is evidence to support the use of all the above discussed techniques independently, the majority of recent studies have demonstrated the benefits of synergistic use of the techniques. It is in combination, mainly that of preoperative lymphoscintigraphy, radioactive tracer and patent blue dye with gamma probe detection, that it is used in dynamic sentinel lymph node biopsy for urological malignancies today.

Use in penile cancer

The use of SLNB in penile cancer was first recommended by Cabanas in 1977 (31). By studying 100 patients he was able to support the existence of a sentinel node in disseminated penile malignancy. He performed lymphangiogram guided sentinel lymph node biopsies on 46 patients concluding that a positive

SLNB was a good indicator that a patient should proceed to full inguinofemoroiliac LND.

Despite support from Cabanas, SLNB fell out of a favor with urologists due to poor reproducibility. It was only after positive experiences from both breast cancer and melanoma, as well as the introduction of patent blue dye injection and radiolabelling, that acceptance of the use and reliability of SLNB in the management of locally advanced penile malignancy was achieved (32-34).

Table 1: SLNB in penile cancer

Author, year (ref)	Cohort size	Methodology	Conclusion
Introduction and Development of technique			
Cabanas et al, 1977(31)	46	Prospective	Feasibility of SLNB in penile cancer (lymphangiograms alone)
Horenblas et al, 2000 (32)	55	Prospective	Feasibility of dynamic SLNB in penile cancer (lymphoscintigraphy, patent blue dye and gamma probe)
Crawshaw et al, 2009 (36)	64	Prospective	Superiority of SLNB combining dynamic SLNB and US guided fine needle aspiration over dynamic SLNB alone which would miss between 5 and 10% metastases
Leijte et al, 2008 (15)	50	Prospective	Superiority of SPECT CT over conventional lymphoscintigraphy
Brouwer et al, 2014 (42)	10	Prospective	Successful use of preoperatively acquired SPECT/CT for intraoperative navigation
Brouwer et al, 2014 (27)	65	Prospective	Superiority of hybrid tracer over patent blue dye
Validating the technique			
Tanis et al, 2002 (33)	90	Prospective	80% sensitivity of dynamic SLNB
Leijte et al, 2007 (35)	150	Retrospective	Reduction in false negative rate and complication rate with introduction of pre-operative FNAC and intra-operative palpation.
Lam et al, 2013 (37)	264	Prospective	DSNB combined with USS demonstrates high sensitivity staging of penile cancer with low false negative rates (94% vs 91%)
Examining outcomes			
Perdona et al, 2005 (38)	48	Retrospective	Dynamic SLNB has similar results to radical inguinal lymphadenectomy but with lower morbidity.
Djajingrat et al, 2013 (40)	1000	Retrospective	Contemporary management of regional lymph nodes has led to an improvement in 5 year survival (92% vs 89%)

Concerns regarding false negative rates remained until 2007 when Leijte et al. demonstrated that the combination of SLNB with ultrasound with or without fine needle aspiration cytology further increased sensitivity (35) , a finding that was supported by Crawshaw et al. in 2009 (36) . A recent paper studying 500 inguinal basins carried out at a tertiary centre, cited a 94% sensitivity per patient when SLNB with ultrasound was used, compared to 91% with blue dye and gamma probe guided SLNB alone (37).

Since the introduction of SLNB, there has been a significant improvement in both morbidity and mortality of patients with penile cancer. A study by Djajadiningrat et al. published in the journal of urology in 2014 looked at the 5 year cancer specific survival of patients with squamous cell carcinoma of the penis. They compared the 5 year cancer survival rate before the introduction of SLNB and after and found a statistically significant difference, 91% compared to 82%, with a p value of 0.021 (38). This was not the first paper with such findings. A Dutch study in 2005, cited 3 year cancer specific survival of patients with positive lymph nodes at 84% for those who underwent SLNB and immediate lymphadenectomy and at 35% for those who had lymph nodes excised only after they became clinically palpable during a period of surveillance. They concluded that SLNB led to earlier identification of positive nodes and that the subsequent early resection directly resulted in a survival benefit (39). The introduction of SLNB has also seen a reduction in morbidity. A study which assessed a group of 48 patients who underwent radical lymphadenectomy, found that 21 suffered with early complications and 18 with late complications, compared to just three early complications seen in the 22 patients who underwent SLNB (40).

SLNB in penile cancer has a high sensitivity and there is well documented, albeit largely retrospective, evidence that it reduces morbidity and mortality. In most patients it allows for more accurate staging but despite this, not all studies have found in its favor. Hungerhuber et al (41), reported on the limited value of sentinel lymph node biopsy in patients with clinically suspicious lymph nodes and it is the existence of such papers that explains why inguinal node dissection with frozen section or preoperative fine needle aspiration remains the preferred procedure in such patients.

Use in pelvic malignancies

Knowledge of the extent of lymphatic invasion in prostate and bladder cancer allows clinicians to stage disease and determine duration and strength of adjuvant therapy. In fact, excision of positive nodes in the absence of distant metastases can even be curative (43). However, views on the use of sentinel nodes in pelvic cancer differ.

Being almost unchanged in size and with microscopic metastases and untraceable using radiological techniques, positive lymph nodes in the pelvis are often difficult to identify. The use of SLNB can address this but controversy surrounding the pattern of lymphatic drainage and the extent of subsequent lymphadenectomy required persists. It is agreed however that with the prostate and bladder being midline structures, lymph may drain to either side indiscriminately and thus that lymph nodes from both sides should be sampled with findings being reported not only per person but per side, as is already the case in cervical cancer (44)

Lymph from the prostate drains via one of three routes, either draining to internal iliac lymph nodes, to external iliac lymph nodes and thus forming a paravesical plexus or travelling posterially to sacral lymph nodes (45). Elucidation of the drainage of prostate cancer cells would allow better management of patients with medium or high risk cancers but studies thus far have failed to clearly define this except to note that tumour location within the gland can have an impact (46).

In 2013, Joniau et al. used a combination of radioactive tracer, planar scintigraphy and SPECT imaging in order to map lymphatic drainage in 74 patients with prostate cancer. They identified sentinel nodes mainly in 5 regions: obturator fossa (25%), internal iliac (25%), external iliac (19%), common iliac (14%), presacral (13%) but noted sentinel nodes also in the pararectal, paravesical and para-aortic regions, in mesenteric fat and at the aortic bifurcation. Their findings reiterated concerns that sentinel nodes are often widely spread suggesting potential for positive lymph nodes in a large number of areas that current lymphadenectomy margins do not account for (47).

Pelvic lymphadenectomy can be broadly categorized into three divisions. 1) Standard lymphadenectomy, which involves resection of all lymphatic and fibrofatty tissue that comprise the external iliac nodes and obturator nodes. 2) Limited lymphadenectomy, which is the removal of the external iliac nodes only, whilst 3) extended lymphadenectomy excises the hypogastric nodes as well as the external iliac and obturator nodes, although some surgeons may also remove the subaortic and presacral nodes (48). The margins of an extended lymphadenectomy remain controversial with two separate studies suggesting that resection at current margins allows for the possibility to undissected lymph nodes and consequently proposing new wider alternatives (47-49). A recent prospective study demonstrated that standard or limited dissection alone would have missed 51.9% and 74.1% of metastatic lymph nodes in a cohort of 200 prostate cancer patients (50). With this and previous studies in mind, prior to SLNB, extended pelvic lymphadenectomy was accepted as the only reliable way for a surgeon to stage the patient's disease despite being associated with higher morbidity when compared to standard lymphadenectomy (51-52).

The decision to proceed to lymphadenectomy in pelvic cancer is made based on validated mathematical algorithms such as Partin tables and Briganti nomograms for prostate cancer (53-54) and nomograms set out by Green et al. and Karakiewicz et al. in bladder cancer (55-56). Such algorithms calculate the likeliness of tumor extending beyond the primary organ and those deemed to have low risk cancer do not proceed to lymphadenectomy. Previously, with no way to accurately differentiate between those with lymph positive disease and those without, all patients calculated to have medium or high risk cancer underwent extended lymphadenectomy despite the associated high morbidity, now such patients undergo SLNB instead. In 2012, Winter et al. questioned the validity of existing algorithms when used with SLNB. They found that previous algorithms (validated on extended pelvic node dissections) were underestimating the incidence of LN involvement (57) and therefore introduced the first LN involvement probability table for use with SLNB.

Table 2: SLNB in prostate cancer

Author, year	Cohort size	Methodology	Conclusion
Introduction and Development of technique			
Augsburg group, 1999 (59)	11	Prospective	Feasibility of SLNB in prostate cancer
Corvin et al, 2006 (68)	28	Prospective	Introduction of Laparoscopic SLNB in prostate cancer
Wynant et al, 2006 (66)	40	Prospective	Immunoscintigraphy can be used to identify positive LNs in prostate cancer
EAU guidelines,2011 (70)	N/A	N/A	Patients with a more than or equal to 7% risk of having lymph node metastases from prostate cancer (calculated using nomograms) should undergo lymph node dissection
Van der Poel, 2011 (26)	11	Prospective	Use of an agent that is both radioactive and fluorescent can be used to optimise LN dissection in prostate cancer
Briganti et al, 2012 (65)	1541	Retrospective	CT is a poor tool for identification of prostate cancer lymph node metastases with high specificity and low sensitivity
Hardie et al, 2013 (67)	18/12	Retrospective	Combining SPECT/CT and MRI increases sensitivity and specificity of identification of lymph node metastases in prostate cancer (sensitivity of CT: 40%, combined 88.9; specificity of CT: 96.7%, combined 98.5%)
Validating the technique			
Holl et al, 2009 (64)	2020	Retrospective	SLNB has 98% intraoperative detection rate with a false negative rate of 6%

Along with penile and breast cancer, the use of a multimodal tracers such as indocyanine green, has been proposed in pelvic cancers. In 2012 Jeschke et al. successfully demonstrated that, using a combination of fluorescence navigation and radiolabelling, technetium labelled indocyanine green provides an equally effective, real time alternative to blue dye, a finding supported by Manny et al in 2014 (58, 24, 25). This is likely to be the future of SLNB in pelvic malignancies.

Prostate cancer

The use of SLNB in prostate cancer was first proposed by the Augsburg group in 1999. They initially examined eleven patients using dynamic lymphoscintigraphy with preoperative radionucleotide being administered transrectally and detected using an intra-operative gamma probe (59). Having successfully demonstrated the success of that technique they performed a larger study with 117 patients, 25 of whom had lymph node metastases and in 24 of the 25 demonstrated 96% sensitivity (60).

Since then many studies have reiterated the high sensitivity and specificity of SLNB in prostate cancer (61-63). The largest of these examined 2020 patients who underwent SLNB over a ten year period. They cited an intra-operative detection rate of 98% when using a preoperative gamma camera and an intra-operative gamma probe. As in penile cancer, false negatives were identified as a potential concern (a 6.2% false negative rate was cited). One potential cause for false negatives were macrometastases blocking lymph node channels and the recommendation was made that all patients being considered for SLNB should first undergo a CT to exclude these (64).

As in penile cancer, SPECT CT was explored as alternative to planar scintigraphy but here with poor results (65). Immunoscintigraphy using monoclonal antibodies was also explored (66), although lymphoscintigraphy combining SPECT CT and MRI was found to be more effective with combined use increasing the sensitivity from 40% with CT alone to 88.9% (67).

Table 3: SLNB in bladder cancer

Author, year	Cohort size	Methodology	Conclusion
Introduction and Development of technique			
Sherif et al, 2001 (71)	13	Prospective	Introduction of SLNB (preoperative scintigraphy, radioactive tracer and patent blue dye) in bladder cancer
Sherif et al, 2006 (73)	6	Prospective	Use of SPECT CT imaging allows for better preoperative idenfication of lymph nodes in patients with bladder cancer than planar imaging
Inoue et al, 2012 (23)	12	Prospective	Introduction of NIRF in bladder cancer
Manny et al, 2014 (24)	10	Prospective	NIRF is feasible for use in robotically assisted procedures
Validating the technique			
Liedberg et al, 2006 (72)	75	Prospective	Use of dynamic SLNB (pre and intra operative scintigraphy, patent blue dye and ex vivo gamma probe examination) along with extended serial sectioning increases bladder cancer nodal staging by 25% but with a false negative rate of 19%

In 2006 Corvin et al. proposed the idea of laparoscopic sentinel node dissection postulating that this would result in lower morbidity, less postoperative pain and shorter hospital stays. Using a gamma camera for preoperative lymph mapping and a laparoscopic gamma probe intra-operatively they proved that laparoscopic sentinel node biopsy can be an acceptable alternative to extended pelvic LND (68), a hypothesis that has since been supported by experience in gynaecological cancers (69).

Bladder cancer

The concept of sentinel node biopsy was introduced to bladder cancer in 2001. Using a combination of scintigraphy, radioactive tracer and blue dye, Sherif et al. identified SNs in thirteen patients awaiting radical cystectomy. After extended pelvic lymphadenectomy has occurred, histopathology confirmed that all of the four positive SNs were detected using the preoperative techniques despite three of them lying outside the standard lymphadenectomy area (71). This study cited a false negative rate of 0% however a larger study looking at 75 patients with invasive bladder cancer quoted 19%, a figured that highlights one of the persistent concerns around SLNB. Despite this, the study successfully demonstrated that the use of pre and intra-operative lymphoscintigraphy, patent blue dye and ex vivo examination with a gamma probe along-side extended serial sectioning improved bladder cancer nodal staging in 25% of patients (72). It is in this form that dynamic SLNB is currently performed in patients with bladder malignancy. However, the introduction of robot assisted sentinel node excision and NIRF is likely to change that in the coming year.

Use in Other Urological Malignancies

Testicular cancer

The use of SNs in testicular malignancy is a relatively new concept. Taking a lead from penile and prostate cancer, Tanis et al. introduced SLNB to testicular cancer in 2002 (74).They demonstrated that preoperative dynamic lymphoscintigraphy using technetium-99m nanocolloid could be used to identify SNs in testicular cancer. In 2005, using a cohort of 22 patients, urologists in Japan built on this further by demonstrating that SLNB using a combination of lymphoscintigraphy using technetium 99m labelled phytate and intra-operative hand held gamma probe yielded detection rate of 95% in stage one testicular cancer(75).

In light of limited evidence in support of its use, and the use of adjuvant chemo and radiotherapy in achieving very low recurrence rates using standard lymphadenectomy , SLNB does not currently have a role in lymph node mapping in testicular malignancy with EAU guidelines suggesting that CT scans be used for staging instead (76).

Table 4: SLNB in testicular cancer

Author, year	Cohort size	Methodology	Conclusion
Introduction and Development of technique			
Tanis et al, 2002 (74)	5	Prospective	Introduction of SLNB in testicular cancer using preoperative lymphoscintigraphy
Satoh et al, 2005 (75)	22	Prospective	Introduction of dynamic SLNB introduced to testicular cancer using preoperative lymphoscintigraphy and hand held gamma probe

Renal cancer

As a malignancy that has a well-recognized haematogenous spread and an unpredictable lymphatic drainage, LND in renal cancer has a limited role (77-79). Metastatic spread has been shown to have a high correlation with size of tumor (80), so with advancing technology allowing for earlier diagnosis of smaller tumors, SLNB may have both a prognostic and therapeutic role to play by identifying and removing nodal disease in patients without distant metastases.

The use of SLNB in renal cancer was first studied in porcine models by Bernie et al (81). Using preoperative radionuclide tracer in combination with US, CT and SPECT scanning and intra-operative hand held gamma probes Bex et al. successfully demonstrated that Bernie's technique could be used to identify SNs in six of eight human patients (16). This was supported by a study of thirteen patients in Sweden which concluded that radioguided surgery in combination with imaging modalities and patent blue dye could identity SNs in renal cancer but that further work was needed to decide the combination of the most efficacious modes of detection (82).At time of writing, LND and extended LND continues to be the accepted management of those with clinically node positive disease without distant metastases or to reduce tumor bulk in those with distant metastases.

Table 5: SLNB in renal cancer

Author, year	Cohort size	Methodology	Conclusion
Introduction and Development of technique			
Bex et al, 2010 (16)	8	Prospective	SLNB has potential for use in renal cancer in humans
Sherif et al, 2012 (82)	13	Prospective	Radioguided surgery and patent blue dye can be used to identify positive nodes in patients with metastatic renal cancer

Conclusion:

Since its introduction SLNB has shown itself to be invaluable in the management of urological cancer. Introduced to improve staging at a lower morbidity cost and initially solely dependent on lymphangiograms, SNLB in its current form has evolved to become a dynamic technique with excellent sensitivity and specificity figures. Here is the overall recommendation:

1. Penile cancer: With high sensitivity and specificity data and strong morbidity and mortality outcomes, we recommend the use of SNLB in penile cancer
2. Prostate Cancer: There is good evidence to support the use of SLNB in prostate cancer but concerns around false negatives persist. This procedure does have potential but in the absence of further outcome data we cannot recommend its use.
3. Bladder cancer: There is good evidence to support the use of SLNB in bladder cancer but concerns around false negatives persist. This procedure does have potential but in the absence of outcome data we cannot recommend its use.
4. Testicular cancer: There is currently no evidence to support the use of SLNB in testicular cancer over other less invasive techniques.
5. Renal cancer: There is currently not enough evidence to support the use of SLNB in renal cancer.

With a role in penile cancer well defined, its feasibility in pelvic cancers well established and with the introduction of NIRF and hybrid tracers, SLNB will continue to improve the management, morbidity and mortality of patients with urological cancers in the future.

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