Review Article

Sentinel lymph node biopsy in bladder cancer: Systematic review and technology update

Michael A. Liss, Jonathan Noguchi[1], Hak J. Lee[1], David R. Vera[2], A. Karim Kader[1]

Department of Urology, University of Texas Health Science Center, San Antonio, TX, Departments of [1]Urology, [2]Radiology and Surgery, University of California, San Diego, California, United States

ABSTRACT

A sentinel lymph node (SLN) is the first lymph node to drain a solid tumor and likely the first place metastasis will travel. SLN biopsy has been well established as a staging tool for melanoma and breast cancer to guide lymph node dissection (LND); its utility in bladder cancer is debated. We performed a systematic search of PubMed for both human and animal studies that looked at SLN detection in cases of urothelial carcinoma of the bladder. We identified a total of nine studies that assessed a variety of imaging techniques to identify SLNs in patients with urothelial carcinoma of the bladder. Eight studies investigated human patients while one looked at animal (dog) models. Seven studies representing 156 patients noted the negative predictive value of the SLN to predict a metastasis free state was 92% (92/100). The SLN biopsy was less accurate in metastatic patients with a positive predictive value of only 77% (43/56) with a false negative range of in individual studies of 0-19%. Clinically, positive nodes routinely do not take up the pharmaceutical agent for SLN. Therefore, SLN biopsy is a promising concept with a 92% negative predictive value; however, the false negative rates are high which may be improved by standardizing populations and indications. Novel technologies are improving the detection of SLN and may provide the surgeon with an improved ability to detect micrometastasis, guide surgery, and reduce patient morbidity.

Key words: Bladder cancer, radiology, sentinel lymph node, technology

INTRODUCTION

Radical cystectomy with pelvic lymphadenectomy and urinary diversion has remained the gold standard for the treatment of localized muscle-invasive and select non-muscle invasive bladder cancers.[1] However, the extent of lymphadenectomy during radical cystectomy has been subject to debate and has fostered several clinical trials (SWOG, NCT01224665).

For correspondence: Prof. Michael A. Liss,
Department of Urology, University of Texas Health Science Center San Antonio, 7703 Floyd Curl Drive,
San Antonio, TX 78229,
United States of America.
E-mail: liss@uthcsca.edu

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Multiple studies have suggested that lymph node density and overall lymph node count may be important prognostic factors leading to an extended node dissection being recommended.[2,3] A more extensive lymph node dissection (LND) will increase the time of a potentially lengthy surgery and may increase complications such as bleeding and lymphocele development.[4] Therefore, many in the community perform limited and some no PLNDs.[5]

The sentinel lymph node (SLN) is the first draining lymph node from the site of cancer and has been previously used to guide the extent of LND in other cancers. As a result, SLN excision may help guide the extent and limits of LND at the time of radical cystectomy possibly improving the quality of this life-saving procedure.[6,7] We performed a systematic review of sentinel LND in bladder cancer and investigate new technologies being evaluated for their role in SLN biopsy.

Evidence acquisition

We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, which is an evidence-based minimum set of items reporting in systematic reviews. We selected articles published and

available online in PubMed in the English language. Only published articles on PubMed were reviewed and we did not communicate directly with other study authors. We did not use or obtain additional datasets. The search was conducted only using PubMed from 1963 up to April 2014 using the search terms: ("Transitional cell carcinoma of the bladder" OR "urothelial cancer of the bladder" OR "bladder cancer") AND ("sentinel lymph node" OR "sentinel lymph node dissection" OR "lymphoscintigraphy" OR "lymphangiography"). We included all primary investigations in the final PubMed search list [Figure 1] and additionally searched the reference lists from these sources to allow for secondary identification of references. We focused on bladder urothelial carcinoma and excluded papers that investigated squamous cell carcinomas, adenocarcinomas, sarcomas, small cell carcinomas and upper urinary tract urothelial carcinomas. Two broad categories were identified in the literature search: (1) Animal and (2) Human studies. We obtained effect estimates including percentage of SLNs detected, the technique used to detect the SLNs and false negative rate (FNR). We summarized these data in one table [Table 1]. Three main steps were used in the data collection process: The initial search of PubMed and manual searches of selected bibliographies, exclusion of abstracts based on title, and exclusion of abstracts based on content [Figure 1]. We did not perform formal quantitative assessments of publication bias. Summary measures for each study are presented in tabular format by listing the percentage of SLNs detected and FNRs as reported in the original studies. We performed descriptive analyses of the data. Due to the heterogeneity of the study populations and reported results, we did not perform formal meta-analyses.

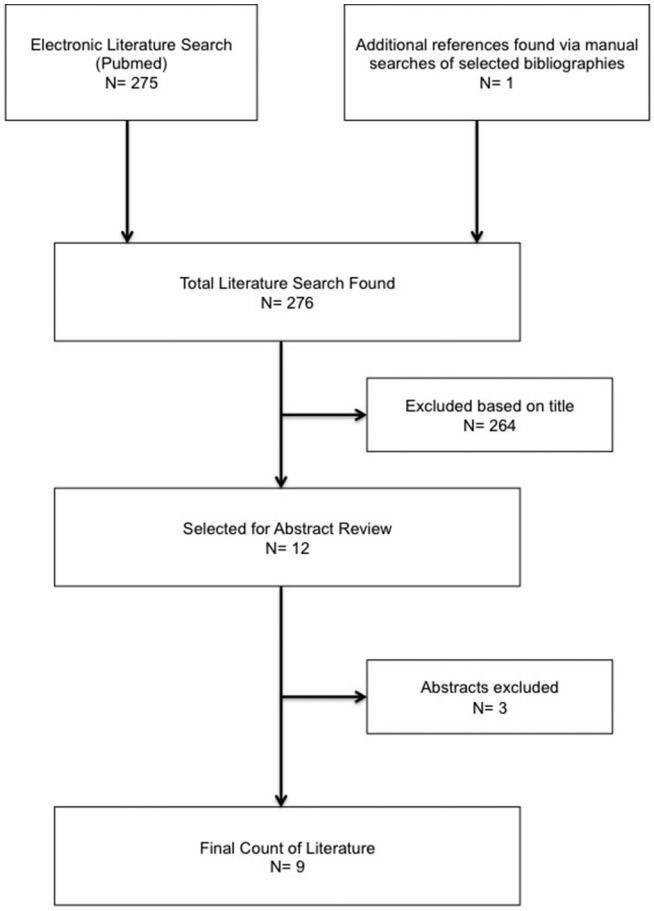

Figure 1: PRISMA study flow diagram

Evidence synthesis

Our initial PubMed search yielded 275 research articles while a further search of references yielded one additional title. Of these, we selected 12 for abstract review and rejected 3 based on our pre-study criteria to yield a total of 9 articles [Figure 1]. The gold standard for injection of the agent is a peritumoral injection prior to the cystectomy via cystoscopy. In order to obtain the full spectrum of lymph nodes, the submucosa and detrusor should be injected. The identification of SLN is performed by the chosen technique of visual or radiological detection. Once the SLN is removed an extended LND should be performed. We provide a summary table of the studies included in the review along with the FNRs. A false-negative SLN was defined as a negative SLN that ultimately had metastatic disease on final pathologic examination of all lymph nodes removed.

Animal studies

We identified one article evaluating the use of near-infrared fluorescent (NIRF) light to detect SLNs in five dogs with naturally occurring invasive transitional cell carcinoma. Knapp *et al.* were able to detect bright fluorescence in the entire node in 25% of SLNs, bright fluorescence in part of the node in 45% of SLNs, and speckled fluorescence inside the node in 30% of SLNs. No false negatives were reported in the study.[8]

Human studies

We identified eight articles that assessed a variety of imaging techniques (including preoperative lymphoscintigraphy, intraoperative blue dye detection, intraoperative dynamic lymphoscintigraphy, indocyanine green (ICG) NIRFI, and SPECT + CT) to identify SLNs in human patients with urothelial carcinoma of the bladder [Table 1].[9-16] There was marked variation in sample size and the imaging techniques used to detect SLNs.

Seven of the eight (88%) human studies found anywhere from 81% to 90% of SLNs, while one study only found 58% of SLNs [Table 1]. The study with low SLN yield had very advanced disease with the majority of patients having T3 and T4 disease. Three studies provided a total percentage of SLNs collectively detected with no distinction between imaging modalities. All three studies utilized preoperative lymphoscintigraphy, intraoperative blue dye detection, and intraoperative dynamic lymphoscintigraphy while the third additionally used combined SPECT + CT. Three other studies

Table 1: Animal and human studies evaluating SLN detection in urothelial cell carcinoma of the bladder

Study	Year	Subject type	No. of patients	Agent injected (amount)	Injection site	Detection technique	Wait time	Sentinel lymph nodes detected	False negative rate
Knapp *et al.* [8]	2007	Animal	5	Human albumin+IRDye 800CW, HSA800, NIRQDs (0.5 ml)	Sub mucosa and serosa	NIRFI	None	Bright fluorescence of entire node: 25% Bright fluorescence of part of node: 45% Speckled fluorescence inside the node: 30%	-
Inoue *et al.* [9]	2012	Human	12	0.25% ICG (0.5 ml)	Peri tumor	ICG FN	5 minutes	58%	100%
Liedberg *et al.* [10]	2003	Human	26	50MBq/ml Albures-99mTc/ Nanocoll Patent Blue	Peri tumor in the detrusor	Preoperative lymphoscintigraphy	-	Cumulative: 81%	4%
						Intraoperative blue dye detection	-		
						Intraoperative dynamic lymphoscintigraphy	-		
Liedberg *et al.* [11]	2006	Human	75	70MBq/ml 99m Tc-nanocolloid (1ml) Patent Blue (1ml)	Peri tumor in the detrusor	Preoperative lymphoscintigraphy	60 minutes	23%	19%
						Intraoperative blue dye detection	-	2/?	
						Intraoperative dynamic lymphoscintigraphy	-	87%	
Malmstrom *et al.* [12]	2002	Human	13	(blue dye)	Peri tumor in the detrusor	Preoperative lymphoscintigraphy	-	Cumulative: 85%	-
						Intraoperative blue dye detection	-		
						Intraoperative Geiger meter detection	-		
Marits *et al.* [13]	2006	Human	14	50MBq/ml Albures-99m Tc (1ml) Patent Blue (1ml)	Peri tumor in the detrusor	Preoperative lymphoscintigraphy	60-240 minutes	Cumulative: 86%	19%
						SPECT+CT	-		
						Intraoperative blue dye detection	-		
						Intraoperative Geiger meter detection	-		
Sherif *et al.* [14]	2001	Human	13	50MBq/ml Albures-99m Tc (1ml) Patent Blue (1ml)	Peri tumor	Preoperative lymphoscintigraphy	60 minutes	67%	0%
						Intraoperative blue dye detection	-	54%	
						Preoperative Geiger meter detection	-	100%	
						Total		85%	
Sherif *et al.* [15]	2006	Human	6	50MBq/ml Albures-99m Tc (1ml) Patent Blue (1ml)	Peri tumor in the detrusor	Preoperative SPECT+CT	120-180 minutes	100%	0%
						Preoperative lymphoscintigraphy	120-180 minutes	10%	
						Intraoperative blue dye detection	-	10%	
						Intraoperative Geiger meter detection	-	52%	
Manny *et al.* [16]	2014	Human	10	2.5mg/ml ICG	Peri tumor in the submucosa and detrusor	ICG NIRFI	30 minutes	90%	0%

provided breakdowns of SLNs detected via each individual imaging modality. Liedberg *et al*.[11] detected SLNs in 23% and 87% of patients using preoperative lymphoscintigraphy and intraoperative dynamic lymphoscintigraphy, respectively. Sherif *et al*.[14] detected SLNs in 67%, 54%, and 100% of patients using preoperative lymphoscintigraphy, intraoperative blue dye detection, and preoperative Geiger meter detection, respectively. In another study, Sherif *et al*.[15] reported SLNs detected in 83% and 33% of patients using combined SPECT + CT and planar lymphoscintigraphy, respectively. Manny *et al*.[16] were able to detect SLNs in 90% of patients.

In our review, the FNR ranged from 0% to 19% across six studies, with three studies reporting a 0% FNR, two studies reporting a 19% FNR, and one study reporting a 4% FNR. One study by Inoue *et al*.[2] reported a 100% FNR using ICG fluorescence navigation (FN). In this particular study, 12 patients undergoing radical cystectomy were injected with 0.5-mL solution of ICG around the tumor. ICG was noted in the lymph channels within 5 minutes as the surgeons focused on the external iliac, obturator and internal iliac nodal regions. The authors reported 189 LNs recovered with 30 LN positive for cancer (15.8%), of which none were highlighted by the ICG. In a contemporary follow up, Manny *et al*.[16] investigated the ICG SLN concept in robotic radical cystectomy of which 30% of lymph nodes were positive for cancer. In this study, they found nodal fluorescence was 100% sensitive, but only 47% specific for the identification of positive lymph nodes. They furthered the analysis with an intention to treat evaluation to predict nodal malignancy and noted that ICG node fluorescence had 75% sensitivity and 52% specificity. Overall 138 patients were investigated for SLNs in bladder cancer and 16 patients (11.6%) had a missed positive lymph node (false negative).

We totaled all patients and divided them into at 2×2 contingency table to describe the test characteristics of the patients reported in the literature [Table 2]. In total, 156 patients underwent SLN detection for which the SLN concept was tested with SLN dissection followed by pelvic LND. SLN dissection was able to detect metastasis in 77% (43/56; i.e., positive predictive value) of patients with metastatic disease. SLN dissection was negative in 92% (92/100; i.e., negative predictive value) of patients without metastasis. The sensitivity and specificity of SLN biopsy in bladder cancer was 84% (43/51) and 87% (92/105), respectively.

Table 2: 2×2 Contingency Table of SLN and metastasis discovered combining all reviewed cases*

	Positive (+) SLN	Negative (-) SLN	
Positive (+) Metastasis	43	13	56
Negative (-) Metastasis	8	92	100
	51	105	156

*The contingency table is a summary of all studies in order to generate a predicted accuracy; however, may not be accurate based on the retrospective nature of the review and different inclusion/exclusion criteria. Sensitivity: 84%, Specificity: 87%, Negative Predictive Value: 92%, Positive Predictive Value: 77%

DISCUSSION

We reviewed seven studies with a total of 156 patients who underwent SLN biopsy with an unadjusted negative predictive value of 92% and a positive predictive value of 77%. The difficulty in SLN usually was encountered with patients who had pT3 cancer or grossly positive lymph nodes changing the pre-test probability for SLN detection to be successful. Unfortunately, the majority of the studies included patients with very advanced bladder cancers. In three studies, more than 50% of patients had pT3 disease and more than 40% of all patients had lymph node metastasis. Moreover, the majority of studies did not mention the clinical lymph node status. Despite the use of patients with advanced stage bladder cancer, the negative predictive value of SLN provides encouraging results to continue investigation of this concept in bladder cancer. We urge that testing of SLN should be performed in the context of a clinical trial in order to standardize patients and perform a risk assessment to account for the probability of metastatic lymph node disease. Moreover, a standardized LND template using the same technique with an appropriately calculated population size is imperative. We hypothesize that the most appropriate group presenting to radical cystectomy is those with pT1 or pT2 cancer with clinically negative lymph nodes.

We also acknowledge that the location of the tumor may be an important determinant regarding the location of SNL and may contribute to FNRs. Therefore, if a clinical trial is conducted, accurate documentation of tumor location is necessary. Other factors that may contribute to SNL rates could be the injection strategy. Some studies inject all around the tumor, while some into the tumor. Additionally, a submucosal vs. detrusor vs. both injection could also impact results.

One of the most important features of SLN biopsy is the FNR for cancer. For example, in breast cancer the SLN is detected, dissected, and sent to pathology for serial sectioning. If a metastasis is noted this will direct the surgeon to perform a LND. However, if the SLN is negative for cancer the surgeon will not perform the LND. Therefore, the SLN biopsy is to guide no further dissection vs. extended dissection and a negative SLN biopsy should predict the positive lymph node status of the patient. The FNR in the individual studies ranged from 0% to 18% and when combining the studies rose to 23%. The poor false positive rate is likely related to the advanced disease in which the SLN testing was performed. Multiple studies site the concept that in a grossly positive lymph node, metastasis will block the

lymph node channel and allow the SLN pharmaceutical to travel to the next level without highlighting the metastatic lymph node.[9,11] Therefore, we stress that the SLN concept would only be accurate in micrometastatic disease or in patients with low risk. High-risk patients should all have an extended pelvic LND.

The level of the LND will impact the negative predictive value, especially in patients who had only pelvic node dissection. A limited pelvic lymphadenectomy may miss positive nodes above the common iliac bifurcation without the pelvic lymph nodes being involved. Unfortunately, none of the current articles reported long-term nodal relapse rates in order to determine if lymph nodes were missed. Therefore, future studies should include long-term follow up of patients to determine nodal recurrence rates, even when extending LNDs are performed.

In breast cancer, the SLN is biopsied and undergoes serial sectioning by pathology which can reveal micrometastatic disease not recognized with traditional post operative lymph node examination not using serial sectioning.[17] Additionally, molecular diagnostics for micrometastatic disease using RT-PCR have now been incorporated into breast cancer nodal staging criteria.[18] Finding micrometastatic or molecular markers of advanced disease may provide prognostic information; however, there currently are limited options regarding chemotherapy for advanced bladder cancer. New modalities are being investigated such as introducing immunotherapy as an early option such as sipuleucel-T for castrate-prostate cancer.[19,20] Martis *et al*. used the SLNs in bladder cancer patients to recover tumor infiltrating lymphocytes (TILs) for expansion and adoptive immunotherapy.[13]

Morbidity is a significant driver regarding the adoption of SNL biopsy in breast and melanoma. Morbidity of the extended LND during an already complex case such as a cystectomy is arguably less morbid than the dissections for breast and melanoma. However, the total length of surgery for cystectomy can be a markedly longer and arguably an arduous task surrounding large vessels of the body. Moreover, bladder cancer patients tend to be older with more comorbid conditions arguing to limit the surgical and anesthesia time. SNL bladder cancer may be beneficial to reduce perioperative complications (lymphocele, DVT formation), reduce operative time, and be performed when otherwise an LND may be omitted.

Technology update

Radiopharmaceuticals

SLN detection has relied on an intricate logistical balance of when to inject the pharmaceutical agent and timing of the dissection. Commonly used nuclear medicine pharmaceuticals include gallium-68 and technetium-99m with or without a dye or fluorescence. A new radiopharmaceutical was recently FDA approved named technetiumTc-99m tilmanocept (Lymphoseek, Navidia Pharmaceuticals, Dublin, OH, USA). Lymphoseek is the first receptor-targeted radiopharmaceutical approved in the United States for use in breast cancer, melanoma, and head and neck cancer.[21-23] Lymphoseek actively binds to CD-206 in lymph nodes and can remain in place for up to 36 hours to allow for PET/CT acquisition and later performance of surgery.[24] PET/CT acquisition prior to surgery has been shown to improve SLN detection in bladder cancer.[15]

Another concept is the use of magnetic properties to avoid radiation in the detection of lymph nodes. Superpargmagnetic iron oxide particles (Sienna+) use a magnetic detector (SentiMag, Endomagnetics, Cambridge, UK) and has been equivalent to Tc-99m for localization of SLN in breast cancer patients.[25] This technology also can be used with MRI localization. While Sienna+ is not receptor targeted, the manufacturer states that that Seinna+ was designed to have better control over particle size that optimizes its retention within lymph nodes compared to the currently used Nanocoll. Nanocoll is not available in the United States and uses human blood products, leaving it susceptible to similar risks as blood transfusions.

Detection equipment

Newer radiation detection equipment such as the Decliplse®SPECT commercialized by SurgicEye (Munich, Germany) can provide three dimensional views of lymph nodes using open and laparoscopic probes.[26] (http://www.surgiceye.com/en/declipseSPECT/laparoscopy.html) This technology relies on the usual nuclear radiotracers and gamma detection.

Additionally, endoscopy can be altered to incorporate new technology such as fluorescence. Many of the current strategies are to use near infrared imaging. Many of the studies in this review used ICG. Visual confirmation of ICG can be performed with various laparoscopic equipments including the FireFly technology incorporated into the DaVinci surgical robotic system (Intuitive Surgical, Sunnyvale, CA, USA).[16] (http://intuitivesurgical.com/company/media/images/firefly.html) Another type of NIR fluorescence is the use of type II quantum dots, which are semiconductor nanocrytals.[27]

CONCLUSION

We identified 156 patients that had been tested using this strategy with a promising 92% negative predictive rate. Ideal candidates for SLN biopsy in future studies are patients with T1 or T2 tumors on resection with clinically negative CT scans prior to cystectomy. Novel technologies are improving the detection of SLN and may provide the surgeon with improved ability to guide lymph node dissection decisions and reduce patient morbidity.

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