World Journal of Nephrology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5527/wjn.v5.i2.182

World J Nephrol 2016 March 6; 5(2): 182-188
ISSN 2220-6124 (online)

Sentinel lymph node biopsy in renal malignancy: The past, present and future

Tharani Mahesan, Alberto Coscione, Ben Ayres, Nick Watkin

Tharani Mahesan, Alberto Coscione, Ben Ayres, Nick Watkin, Department of Urology, St George's Hospital, London SW17 0QT, United Kingdom

Author contributions: All authors equally contributed to this paper with conception and design of the study, literature review and analysis, drafting and critical revision and editing, and final approval of the final version.

Conflict-of-interest statement: No potential conflicts of interest. No financial support.

Correspondence to: Nick Watkin, Consultant Urologist, Department of Urology, St George's Hospital, Blackshaw Road, Tooting, London SW17 0QT, United Kingdom. nick.watkin@stgeorges.nhs.uk
Telephone: +44-208-6721255
Fax: +44-208-4876304

Received: August 22, 2015
Peer-review started: August 25, 2015
First decision: October 30, 2015
Revised: December 19, 2015
Accepted: January 8, 2016
Article in press: January 11, 2016
Published online: March 6, 2016

Abstract

Sentinel lymph node biopsy (SLNB) is now an established technique in penile and pelvic cancers, resulting in a lower mortality and morbidity when compared with the traditional lymph node dissection. In renal cancer however, despite some early successes for the SLNB technique, paucity of data remains a problem, thus lymph node dissection and extended lymph node dissection remain the management of choice in clinically node positive patients, with surveillance of lymph nodes in those who are clinically node negative. SLNB is a rapidly evolving technique and the introduction of new techniques such as near infra-red fluorescence optical imaging agents and positron emission tomography/computed tomography scans, may improve sensitivity. Evidence in support of this has already been recorded in bladder and prostate cancer. Although the lack of large multi-centre studies and issues around false negativity currently prevent its widespread use, with evolving techniques improving accuracy and the support of large-scale studies, SLNB does have the potential to become an integral part of staging in renal malignancy.

Key words: Sentinel lymph node biopsy; Dynamic sentinel node; Renal malignancy; Lymphoscintigraphy; Near infra-red fluorescence; Penile cancer; Lymphatic drainage

Core tip: A number of studies have examined the use of sentinel lymph node biopsy in urogenital malignancies. In penile and prostate cancer it has been found to be a valuable tool to aid staging and accurately predict prognosis. Its use in renal cancer is poorly explored and would benefit from a better understanding of the lymphatic drainage of the kidney. It is also proposed that modifications of the technique such as use of positron emission tomography/computed tomography scanning and near infra-red fluorescence optical imaging agents may further improve the technique making it a feasible option for use in renal malignancy.

Mahesan T, Coscione A, Ayres B, Watkin N. Sentinel lymph node biopsy in renal malignancy: The past, present and future. *World J Nephrol* 2016; 5(2): 182-188 Available from: URL: http://www.

wjgnet.com/2220-6124/full/v5/i2/182.htm DOI: http://dx.doi.org/10.5527/wjn.v5.i2.182

INTRODUCTION

Renal cancer is now the 8th most common cancer in the United Kingdom and its incidence is rising[1]. Advancements in imaging modalities and easy access to ultrasounds mean that tumours are often detected earlier and consequently with a smaller size than previously. Whilst size of tumour and haematogenous spread are acknowledged to be proportionately linked, small tumours do have the potential for early lymphatic spread and distant metastases[2]. Unlike other urogenital malignancies such as penile cancer, lymphatic spread in renal cancer is often unpredictable making it unsuitable for en-block lymph node dissection[3-5].

Sentinel lymph node biopsy (SLNB) offers a well-recognised alternative to lymph node dissection and is already widely used in melanoma and breast cancer[6,7]. It is also already an accepted part of management in certain urological malignancies such as penile and pelvic malignancy[8-12]. Associated with a lower mortality and morbidity cost than the traditional alternative, it still offers clinicians the opportunity to stage disease and equally importantly, to identify patients in whom tumour resection alone may not be curative[10,13,14].

In renal cancer however, lymph node dissection and extended lymph node dissection still remain the management of choice in clinically node positive patients with renal malignancy, with surveillance of lymph nodes in those who are clinically node negative[15]. Here, we examine the potential of SLNB in renal malignancy and some of the techniques that may be implemented in the future.

LYMPH DRAINAGE AND THE KIDNEY

The use and success of SLNB is reliant on the ability to reliably predict the lymphatic drainage of the organ and the dissemination of disease in a stepwise fashion. Of all urogenital malignancies, penile cancer exhibits the most reliable lymphatic drainage, allowing us to predict with some accuracy areas where the sentinel nodes will reside[16]. Conversely, renal cancer, with the potential for both haematogenous and lymphatogenous spread is the least reliable, and it is only by using a mixture of cadaveric and sentinel lymph node mapping that basic patterns have been observed[17]. Lymph node involvement in the absence of other metastases is common in pelvic and penile cancers, but uncommon in renal cancer.

Lymphatic drainage of the kidney can be grouped into three categories relative to their position to the renal vein: Anterior, posterior and intravascular. From the right kidney, the anterior bundles drain to the paracaval, precaval, retrocaval and interaortacaval nodes. Importantly the retrocaval nodes provide a route of entry to the thoracic duct, facilitating more distant lymphatic spread. Posterior bundles drain to paracaval, retrocaval and interaortocaval nodes. Drainage from the intravascular bundles remains poorly understood[18-20].

Different from the right kidney, anterior bundles in the left kidney drain to the para-aortic and pre-aortic nodes, while posterior bundles drain to the para-aortic and retro-aortic nodes. In the case of the left kidney, it is direct from the posterior bundle, rather than *via* nodes from the anterior bundle that connection to the thoracic duct is made[17,21,22]. Lymphatic drainage from both kidneys may also run to the retroperitoneal lymph nodes, and from these spread to the thoracic duct. Overall, lymph node involvement is reported at rates of 4%-5% and considered to be a poor prognostic indicator[23,24].

Despite not offering therapeutic benefit in renal malignancy, SLNB does offer the opportunity to histologically confirm the presence of positive nodes without full lymphadenectomy. In the absence of such clarity, the current European recommendation is to wait for nodes to become clinically palpable before excision, this can have significant implications on mortality. In penile cancer, since the introduction of SLNB and immediate lymphadenectomy for node positive patient, 3 year cancer survival increased to 84%, compared to just 35% for those who had lymph nodes excised only after they became clinically palpable[25]. A further study reported a 5 year cancer survival of 91% for patients with penile squamous cell carcinoma after introduction of SLNB, compared to 82% before its introduction[13].

THE SENTINEL NODE CONCEPT IN UROGENITAL CANCER: HOW DID WE GET HERE?

The concept of a sentinel node was introduced by Halstead who proposed that tumour cells spread from the primary lesion sequentially along the lymph chain, only spreading beyond the first node once it has been overwhelmed by tumour[26]. It was Gould however, in a paper on parotid malignancy, who initially described these first nodes as sentinel nodes[27].

When SLNB was first introduced, sentinel nodes were identified solely using either intraoperative or preoperative lymphangiograms. This was first trialled for urogenital malignancy by Cabanas[28] in 1977. In a study of 100 patients he successfully proved the existence of a sentinel node in disseminated penile malignancy. In 46 of those patients he was able to perform lymphangiogram guided SLNB and from this concluded that a positive SLNB was a good indicator for further surgical intervention in the form of a full regional lymph node dissection[28]. However, this technique was associated with a high failure rate and poor reducibility as nodes were often difficult to identify and locate and the technique did not allow for anatomical variation between patients[29].

This concern was addressed with the introduction of blue dye allowing for cutaneous lymph node mapping. Once injected at the primary tumour site, the blue dye travels along the lymphatic chain to the sentinel node, making it easier for the surgeon to identify. Introduced in 1989 for melanoma, cutaneous lymph node mapping now has since been explored for use in breast, penile and cervical cancer[30-34].

The concept of cutaneous mapping was rapidly followed by the introduction of radiolabelled racer using a gamma probe. Proposed by the team at Vermont medical centre, their study, on 16 feline models, found that the use of radiolabelled tracer detected with a gamma probe was comparable to blue dye tracer but additionally allowed the surgeon to confirm excision of the correct node and determine possible presence of residual lymph nodes[34].

In 2000, Horenblas *et al*[32] examined the feasibility of dynamic SLNB (DSNB) in penile cancer. Using a combination of lymphoscintigraphy, patent blue dye and a gamma probe they concluded that DSNB held potential as a promising staging technique[35]. Their conclusion, supported by Tanis *et al*[8] who cited an 80% sensitivity for this procedure, cemented the role of DSNB in penile cancer. It was in this form that the Augsberg group introduced DSNB to prostate cancer[36]. They successfully demonstrated the validity of DSNB for use in prostate cancer and in a further study of 117 patients, the same group demonstrated a sensitivity of 96% for the procedure, a validation replicated in bladder cancer in Sherif *et al*[37]'s study of 13 patients[38]. They concluded that not only can DSNB be used to identify sentinel nodes in patients with known bladder cancer but that it has the additional advantage over traditional lymphadenectomy of identifying nodes outside the standard lymphadenectomy areas.

TAILORING THE SENTINEL NODE CONCEPT FOR RENAL CANCER

It was Bernie *et al*[39] in 2003 who introduced DSNB to renal cancer. Combining the use of blue dye and intraoperative gamma probes they successfully demonstrated that in 40 porcine models, excised sentinel nodes exhibited an increased radioactive count when compared to controls[39].

In 2010 Bex *et al*[40] continued the work of Bernie, confirming the use of sentinel node mapping in renal malignancy in human models. They successfully demonstrated that the use of pre-operative lymphoscintigraphy combined with the injection of technetium 99m under either ultrasonography (US) or computed tomography (CT) guidance can be used to identify sentinel nodes in renal malignancy.

Single-photon emission computed tomography (SPECT) CT combines single proton emission computed tomography with CT in order to provide more precise information about the presence and location of sentinel nodes. The concept of such anatomical fusion imaging, as an alternative to planar lymphoscintography was first introduced for use in prostate cancer in 2005. That study successfully demonstrated that images from CT scan and SPECT scanning could be superimposed in all 12 of the patients studied and successfully identified 87% of lymph nodes[41]. A Swedish study in 2006, expanded this work to bladder cancer when they successfully demonstrated that SPECT CT scanning detected 21 sentinel nodes in five patients, compared to just two with planar lymphoscintography[42].

In 2011, Sherif *et al*[37] trialled SPECT CT for use in lymph node mapping for renal cancer. Their study of 13 patients introduced pre-operative SPECT scanning to lymph node mapping in renal malignancy. They combined lymphoscintigraphy and SPECT CT imaging, with both radiolabelled tracer and patent blue dye in order to identify sentinel nodes. This study successfully detected 32 sentinel nodes in 10 of 11 patients, 28 of which were detected by the use of radiolabelled tracer. The patent blue dye was used in 8 patients but only identified sentinel nodes in one patient[43].

SLNB IN RENAL CANCER: WHERE NEXT?

SLNB in renal cancer, still lags well behind its penile and pelvic counterpart and has some way to go before a widespread implementation can be considered. In addition to concerns about small studies, concerns about sensitivity-in particular false negatives, and patient selection remain.

Renal cancer is not alone in these concerns, with many papers initially raising similar concerns around false negative rates in penile and pelvic cancers. A study of 2020 patients undergoing SLNB for prostate cancer cited a false a negative rate of 6.2%, whilst a study in 2011 of SLNB in penile malignancy cited an even higher rate of 15%[44,45]. In both cases, figures are controversial and highly variable, and measures such as pre SLNB CT to exclude macrometastases, a potential cause of false negatives, have been implemented[8,44,46,47]. More importantly, SLNB has overcome these problems to become part of the accepted management for both penile and pelvic cancers.

Below, we discuss alternative or additional techniques that are currently being explored in other urogenital malignancies. These may hold the solution for the redemption of SLNB for use in renal malignancy.

IMPROVING SENSITIVITY

Near infra-red fluorescence optical imaging agents (NIRF) is a non-radioactive, more penetrative alternative to radiolabelled tracers and patent blue, which may provide the solution to concerns around sensitivity. First introduced in 2003 in mice models, it was initially studied in breast cancer, with Melancon *et al*[47] successfully demonstrating that NIRF provided a superior alternative

to T1 weighted MR, identifying all six cervical nodes, compared to just four[48]. The first use of NIRF in urogenital malignancy was in 2011, when lymphatic pathways in prostate cancer were mapped with indocyanine[49]. NIRF has since been used bladder cancer and in robot assisted SLNB in both bladder and prostate cancer[50,51].

The introduction and acknowledgement of NIRF as a tracer, has led to the potential for a hybrid tracer, combining the fluorescence of NIRF with the well-established pharmacokinetics and bio-distribution of radiocolloids such as technetium 99m. The use of a multimodal tracer was first studied in mice in 2011[52]. Since then its use has been studied in prostate and melanoma with the finding that it is equally effective tracer with faster distribution than blue dye[53,54]. Similarly in penile cancer, a study of 65 patients, cited an increased sensitivity (96.8%) compared to patent blue dye alone (55.7%)[55].

The use of positron emission tomography/CT (PET/CT) as part of the SLNB procedure has also been explored as a means of improving false negative rates. Here fluorodeoxyglucose PET/CT scan was performed routinely preoperatively in patients undergoing SLNB for penile squamous cell carcinoma. In a study of 129 patients, involving 254 basins, use of both techniques, reduced false negative rates to 5.6%, proving that it may have potential to improve the SLNB technique[56]. PET/CT has been more vigorously explored in breast cancer, where a study of 191 patients concluded that it had the highest specificity of Ultrasound and MRI, but that it required all 3 in combination to reach the highest sensitivity[57]. There is no current available work on its role in SLNB for renal cancer and its impact here remains to be seen.

IMPROVING PATIENT SELECTION

Patient selection remains one of the challenges of lymph node disease. At present all patients who are clinically node positive in all urological malignancy undergo full regional lymphadenectomy. Historically, those with node negative disease in penile and bladder cancer were undergoing SLNB despite concerns that a high false negative rate means that disease may go unidentified. To address this, colleagues in the Netherlands introduced an ultrasound scan for patients with clinically node negative disease. Any suspicious nodes visualised underwent fine needle aspiration and cytology. Those with a negative FNAC or absence of suspicious nodes proceeded to SLNB procedure, consisting of lymphoscintigraphy and injection of patient blue, whilst those with a positive FNAC proceeded straight to inguinal lymph node dissection. The introduction of the pre-operative ultrasound, combined with a decision to explore all groins after lymphoscintigraphy, rather than those with suspicious nodes, reduced their false negative rate from 19.2% to 4.8%[58]. Similarly, a study of 500 inguinal basins, cited a 91% sensitivity rate with blue dye and radiolabelled tracer, which rose to a 94% with the introduction of the pre-operative ultrasound[59].

An alternative solution would be the introduction of mathematical algorithms such as the Partin table and Briganti nomograms used in prostate malignancy. These algorithms calculate the likelihood of lymph node involvement, and only those with a high calculated risk proceed to lymphadenectomy[60,61]. The concept of identifying risk factors for positive lymph nodes in renal malignancy was first introduced in 2004 but it was Hutterer who created the first nomogram in 2007[62,63]. In 2015 local symptoms, clinical node stage and lactate dehydrogenase were identified as independent predictors of lymph node disease, using all of these as determining factors in their nomogram which they cited as having a concordance index of 0.89[64]. Further work and external validation has yet to be published and there is no current evidence to suggest that it could be extrapolated for an incorporation into use for SLNB.

IMPROVING MORBIDITY

One of the acknowledged benefits of SLNB when compared to the traditional alternative of lymphadenectomy is a reduced morbidity[65]. This could be reduced further with the introduction of laparoscopic sentinel nodes, a theory explored by Kamprath *et al*[66] in 2000, when they proved that laparoscopic sentinel nodes in cervical cancer would result in lower morbidity and also reduce post-operative pain, with shorter duration of stay when compared to an open procedure. Such a procedure has already been trialled in prostate cancer with good effect[67].

Similarly, the SLNB has the potential to be performed robotically. This concept was explored by Rossi *et al*[68], who concluded that a robotic lymph mapping procedure for use in endometrial and cervical cancer was not only feasible, but an efficient and reliable technique. A further study successfully used NIRF to identify sentinel drainage in pelvic cancers in robot assisted procedures[50,51]. Whilst no direct comparisons have been made between traditional SLNB techniques and the robotic technique, a study comparing robotic and open surgical staging for endometrial cancer, demonstrated a lower incidence of post op ileus, duration of say, infection and cardiopulmonary complications in patients who underwent a robot procedure whilst still achieving similar lymph node yields[69]. If such findings can be extrapolated to SLNB and in particular to renal cancer, this may have a positive impact on morbidity.

CONCLUSION

SLNB offers the potential for accurate staging in renal cancer, the accuracy of which may have huge implications for prognosis. In its current form however, SLNB lacks not only the support of large, multi-centre studies but, like its predecessors in penile and pelvic malignancy, continues to be plagued by concerns around high false negative rates. With the investigation

and implementation of enhanced techniques, and support from large cohort size studies, SLNB does have the potential to become an integral part of staging in renal malignancy.

REFERENCES

1 Cancer research UK: statistics on kidney cancer. Available from: URL: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/kidney-cancer

2 **Matsuyama H**, Hirata H, Korenaga Y, Wada T, Nagao K, Yamaguchi S, Yoshihiro S, Naito K. Clinical significance of lymph node dissection in renal cell carcinoma. *Scand J Urol Nephrol* 2005; **39**: 30-35 [PMID: 15764268 DOI: 10.1080/00365590410018701]

3 **Blom JH**, van Poppel H, Maréchal JM, Jacqmin D, Schröder FH, de Prijck L, Sylvester R. Radical nephrectomy with and without lymph-node dissection: final results of European Organization for Research and Treatment of Cancer (EORTC) randomized phase 3 trial 30881. *Eur Urol* 2009; **55**: 28-34 [PMID: 18848382 DOI: 10.1016/j.eururo.2008.09.052]

4 **Barrisford GW**, Gershman B, Blute ML. The role of lymphadenectomy in the management of renal cell carcinoma. *World J Urol* 2014; **32**: 643-649 [PMID: 24723269]

5 **Phillips CK**, Taneja SS. The role of lymphadenectomy in the surgical management of renal cell carcinoma. *Urol Oncol* 2003; **22**: 214-223; discussion 223-224 [PMID: 15271320 DOI: 10.1016/j.urolonc.2004.04.028]

6 **Bluemel C**, Herrmann K, Giammarile F, Nieweg OE, Dubreuil J, Testori A, Audisio RA, Zoras O, Lassmann M, Chakera AH, Uren R, Chondrogiannis S, Colletti PM, Rubello D. EANM practice guidelines for lymphoscintigraphy and sentinel lymph node biopsy in melanoma. *Eur J Nucl Med Mol Imaging* 2015; **42**: 1750-1766 [PMID: 26205952 DOI: 10.1007/s00259-015-3135-1]

7 **Kroon BK**, Horenblas S, Meinhardt W, van der Poel HG, Bex A, van Tinteren H, Valdés Olmos RA, Nieweg OE. Dynamic sentinel node biopsy in penile carcinoma: evaluation of 10 years experience. *Eur Urol* 2005; **47**: 601-606; discussion 606 [PMID: 15826750 DOI: 10.1016/j.eururo.2004.11.018]

8 **Tanis PJ**, Lont AP, Meinhardt W, Olmos RA, Nieweg OE, Horenblas S. Dynamic sentinel node biopsy for penile cancer: reliability of a staging technique. *J Urol* 2002; **168**: 76-80 [PMID: 12050496 DOI: 10.1097/00005392-200207000-00019]

9 **Perdonà S**, Autorino R, De Sio M, Di Lorenzo G, Gallo L, Damiano R, D'Armiento M, Gallo A. Dynamic sentinel node biopsy in clinically node-negative penile cancer versus radical inguinal lymphadenectomy: a comparative study. *Urology* 2005; **66**: 1282-1286 [PMID: 16360457 DOI: 10.1016/j.urology.2005.06.085]

10 **Liedberg F**, Chebil G, Davidsson T, Gudjonsson S, Månsson W. Intraoperative sentinel node detection improves nodal staging in invasive bladder cancer. *J Urol* 2006; **175**: 84-88; discussion 88-89 [PMID: 16406877 DOI: 10.1097/00005392-200601000-00020]

11 **Holl G**, Dorn R, Wengenmair H, Weckermann D, Sciuk J. Validation of sentinel lymph node dissection in prostate cancer: experience in more than 2,000 patients. *Eur J Nucl Med Mol Imaging* 2009; **36**: 1377-1382 [PMID: 19430782 DOI: 10.1007/s00259-009-1157-2]

12 **Djajadiningrat RS**, Graafland NM, van Werkhoven E, Meinhardt W, Bex A, van der Poel HG, van Boven HH, Valdés Olmos RA, Horenblas S. Contemporary management of regional nodes in penile cancer-improvement of survival? *J Urol* 2014; **191**: 68-73 [PMID: 23917166 DOI: 10.1016/j.juro.2013.07.088]

13 **Lont AP**, Horenblas S, Tanis PJ, Gallee MP, van Tinteren H, Nieweg OE. Management of clinically node negative penile carcinoma: improved survival after the introduction of dynamic sentinel node biopsy. *J Urol* 2003; **170**: 783-786 [PMID: 12913697 DOI: 10.1097/01.ju.0000081201.40365.75]

14 **Ljungberg B**, Bensalah K, Canfield S, Dabestani S, Hofmann F, Hora M, Kuczyk MA, Lam T, Marconi L, Merseburger AS, Mulders P, Powles T, Staehler M, Volpe A, Bex A. EAU guidelines on renal cell carcinoma: 2014 update. *Eur Urol* 2015; **67**: 913-924 [PMID: 25616710 DOI: 10.1016/j.eururo.2015.01.005]

15 Cancer research UK: Kidney cancer. Available from: URL: http://www.cancerresearchuk.org/about-cancer/type/kidney-cancer/about/types-of-kidney-cancer

16 **Horenblas S**. Sentinel lymph node biopsy in penile carcinoma. *Semin Diagn Pathol* 2012; **29**: 90-95 [PMID: 22641958 DOI: 10.1053/j.semdp.2011.08.001]

17 **Karmali RJ**, Suami H, Wood CG, Karam JA. Lymphatic drainage in renal cell carcinoma: back to the basics. *BJU Int* 2014; **114**: 806-817 [PMID: 24841690 DOI: 10.1111/bju.12814]

18 **Parker AE**. Studies on the main posterior lymph channels of the abdomen. *Am J Anat* 1935; **56**: 409–443 [DOI: 10.1002/aja.1000560305]

19 **Kubik S**. Anatomy of the lymphatic system. In: Foldi M, Foldi E, editors. Foldi's Textbook of Lymphology. 2nd ed. Munich: Urban and Fischer, 2006: 1-149

20 **Harrison DA**, Clouse ME. Normal anatomy. In: Clouse M, Wallace S, editors. Lymphatic Imaging, Baltimore: Williams and Wilkins, 1985: 15-94

21 **Assouad J**, Riquet M, Berna P, Danel C. Intrapulmonary lymph node metastasis and renal cell carcinoma. *Eur J Cardiothorac Surg* 2007; **31**: 132-134 [PMID: 17118670 DOI: 10.1016/j.ejcts.2006.10.025]

22 **Assouad J**, Riquet M, Foucault C, Hidden G, Delmas V. Renal lymphatic drainage and thoracic duct connections: implications for cancer spread. *Lymphology* 2006; **39**: 26-32 [PMID: 16724507]

23 **Patard JJ**. Prognostic and biological significance of lymph node spreading in renal cell carcinoma. *Eur Urol* 2006; **49**: 220-222 [PMID: 16426737 DOI: 10.1016/j.eururo.2005.12.025]

24 **Capitanio U**, Jeldres C, Patard JJ, Perrotte P, Zini L, de La Taille A, Ficarra V, Cindolo L, Bensalah K, Artibani W, Tostain J, Valeri A, Zigeuner R, Méjean A, Descotes JL, Lechevallier E, Mulders PF, Lang H, Jacqmin D, Karakiewicz PI. Stage-specific effect of nodal metastases on survival in patients with non-metastatic renal cell carcinoma. *BJU Int* 2009; **103**: 33-37 [PMID: 18990161 DOI: 10.1111/j.1464-410X.2008.08014.x]

25 **Kroon BK**, Horenblas S, Lont AP, Tanis PJ, Gallee MP, Nieweg OE. Patients with penile carcinoma benefit from immediate resection of clinically occult lymph node metastases. *J Urol* 2005; **173**: 816-819 [PMID: 15711276 DOI: 10.1097/01.ju.0000154565.37397.4d]

26 **Halsted WS**. I. The Results of Radical Operations for the Cure of Carcinoma of the Breast. *Ann Surg* 1907; **46**: 1-19 [PMID: 17861990 DOI: 10.1097/00000658-190707000-00001]

27 **Gould EA**, Winship T, Philbin PH, Kerr HH. Observations on a "sentinel node" in cancer of the parotid. *Cancer* 1960; **13**: 77-78 [PMID: 13828575]

28 **Cabanas RM**. An approach for the treatment of penile carcinoma. *Cancer* 1977; **39**: 456-466 [PMID: 837331]

29 **Pettaway CA**, Pisters LL, Dinney CP, Jularbal F, Swanson DA, von Eschenbach AC, Ayala A. Sentinel lymph node dissection for penile carcinoma: the M. D. Anderson Cancer Center experience. *J Urol* 1995; **154**: 1999-2003 [PMID: 7500444 DOI: 10.1097/00005392-199512000-00004]

30 **D'Angelo-Donovan DD**, Dickson-Witmer D, Petrelli NJ. Sentinel lymph node biopsy in breast cancer: a history and current clinical recommendations. *Surg Oncol* 2012; **21**: 196-200 [PMID: 22237143 DOI: 10.1016/j.suronc.2011.12.005]

31 **Giuliano AE**, Kirgan DM, Guenther JM, Morton DL. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. *Ann Surg* 1994; **220**: 391-398; discussion 398-401 [PMID: 8092905 DOI: 10.1097/00000658-199409000-00015]

32 **Horenblas S**, Jansen L, Meinhardt W, Hoefnagel CA, de Jong D, Nieweg OE. Detection of occult metastasis in squamous cell carcinoma of the penis using a dynamic sentinel node procedure. *J Urol* 2000; **163**: 100-104 [PMID: 10604324 DOI: 10.1097/00005392-200001000-00025]

33 **Bilchik AJ**, Giuliano A, Essner R, Bostick P, Kelemen P, Foshag LJ, Sostrin S, Turner RR, Morton DL. Universal application of intraoperative lymphatic mapping and sentinel lymphadenectomy

in solid neoplasms. *Cancer J Sci Am* 1998; **4**: 351-358 [PMID: 9853133]
34 **Schwendinger V**, Müller-Holzner E, Zeimet AG, Marth C. Sentinel node detection with the blue dye technique in early cervical cancer. *Eur J Gynaecol Oncol* 2006; **27**: 359-362 [PMID: 17009626]
35 **Alex JC**, Krag DN. The gamma-probe-guided resection of radiolabeled primary lymph nodes. *Surg Oncol Clin N Am* 1996; **5**: 33-41 [PMID: 8789492 DOI: 10.1016/0960-7404(93)90001-F]
36 **Mariani G**, Gipponi M, Moresco L, Villa G, Bartolomei M, Mazzarol G, Bagnara MC, Romanini A, Cafiero F, Paganelli G, Strauss HW. Radioguided sentinel lymph node biopsy in malignant cutaneous melanoma. *J Nucl Med* 2002; **43**: 811-827 [PMID: 12050328]
37 **Sherif A**, De La Torre M, Malmström PU, Thörn M. Lymphatic mapping and detection of sentinel nodes in patients with bladder cancer. *J Urol* 2001; **166**: 812-815 [PMID: 11490224 DOI: 10.1016/S0022-5347(05)65842-9]
38 **Wawroschek F**, Vogt H, Weckermann D, Wagner T, Harzmann R. The sentinel lymph node concept in prostate cancer - first results of gamma probe-guided sentinel lymph node identification. *Eur Urol* 1999; **36**: 595-600 [PMID: 10559614 DOI: 10.1159/000020054]
39 **Bernie JE**, Zupkas P, Monga M. Intraoperative mapping of renal lymphatic drainage: technique and application in a porcine model. *J Endourol* 2003; **17**: 235-237 [PMID: 12816587 DOI: 10.1089/089277903765444375]
40 **Bex A**, Vermeeren L, de Windt G, Prevoo W, Horenblas S, Olmos RA. Feasibility of sentinel node detection in renal cell carcinoma: a pilot study. *Eur J Nucl Med Mol Imaging* 2010; **37**: 1117-1123 [PMID: 20111964 DOI: 10.1007/s00259-009-1359-7]
41 **Kizu H**, Takayama T, Fukuda M, Egawa M, Tsushima H, Yamada M, Ichiyanagi K, Yokoyama K, Onoguchi M, Tonami N. Fusion of SPECT and multidetector CT images for accurate localization of pelvic sentinel lymph nodes in prostate cancer patients. *J Nucl Med Technol* 2005; **33**: 78-82 [PMID: 15930020]
42 **Sherif A**, Garske U, de la Torre M, Thörn M. Hybrid SPECT-CT: an additional technique for sentinel node detection of patients with invasive bladder cancer. *Eur Urol* 2006; **50**: 83-91 [PMID: 16632191 DOI: 10.1016/j.eururo.2006.03.002]
43 **Sherif AM**, Eriksson E, Thörn M, Vasko J, Riklund K, Ohberg L, Ljungberg BJ. Sentinel node detection in renal cell carcinoma. A feasibility study for detection of tumour-draining lymph nodes. *BJU Int* 2012; **109**: 1134-1139 [PMID: 21883833 DOI: 10.1111/j.1464-410X.2011.10444.x]
44 **Kirrander P**, Andrén O, Windahl T. Dynamic sentinel node biopsy in penile cancer: initial experiences at a Swedish referral centre. *BJU Int* 2013; **111**: E48-E53 [PMID: 22928991 DOI: 10.1111/j.1464-410X.2012.11437.x]
45 **Kroon BK**, Horenblas S, Estourgie SH, Lont AP, Valdés Olmos RA, Nieweg OE. How to avoid false-negative dynamic sentinel node procedures in penile carcinoma. *J Urol* 2004; **171**: 2191-2194 [PMID: 15126783 DOI: 10.1097/01.ju.0000124485.34430.15]
46 **Kroon BK**, Valdés Olmos R, Nieweg OE, Horenblas S. Non-visualization of sentinel lymph nodes in penile carcinoma. *Eur J Nucl Med Mol Imaging* 2005; **32**: 1096-1099 [PMID: 15875177 DOI: 10.1007/s00259-005-1822-z]
47 **Melancon MP**, Wang Y, Wen X, Bankson JA, Stephens LC, Jasser S, Gelovani JG, Myers JN, Li C. Development of a macromolecular dual-modality MR-optical imaging for sentinel lymph node mapping. *Invest Radiol* 2007; **42**: 569-578 [PMID: 17620940 DOI: 10.1097/RLI.0b013e31804f5a79]
48 **Inoue S**, Shiina H, Arichi N, Mitsui Y, Hiraoka T, Wake K, Sumura M, Honda S, Yasumoto H, Urakami S, Matsubara A, Igawa M. Identification of lymphatic pathway involved in the spreading of prostate cancer by fluorescence navigation approach with intraoperatively injected indocyanine green. *Can Urol Assoc J* 2011; **5**: 254-259 [PMID: 21801682 DOI: 10.5489/cuaj.10159]
49 **Inoue S**, Shiina H, Mitsui Y, Yasumoto H, Matsubara A, Igawa M. Identification of lymphatic pathway involved in the spread of bladder cancer: Evidence obtained from fluorescence navigation with intraoperatively injected indocyanine green. *Can Urol Assoc J* 2012; **7**: E322-E328 [PMID: 23069700]
50 **Manny TB**, Hemal AK. Fluorescence-enhanced robotic radical cystectomy using unconjugated indocyanine green for pelvic lymphangiography, tumor marking, and mesenteric angiography: the initial clinical experience. *Urology* 2014; **83**: 824-829 [PMID: 24680450 DOI: 10.1016/j.urology.2013.11.042]
51 **Manny TB**, Patel M, Hemal AK. Fluorescence-enhanced robotic radical prostatectomy using real-time lymphangiography and tissue marking with percutaneous injection of unconjugated indocyanine green: the initial clinical experience in 50 patients. *Eur Urol* 2014; **65**: 1162-1168 [PMID: 24289911 DOI: 10.1016/j.eururo.2013.11.017]
52 **van Leeuwen AC**, Buckle T, Bendle G, Vermeeren L, Valdés Olmos R, van de Poel HG, van Leeuwen FW. Tracer-cocktail injections for combined pre- and intraoperative multimodal imaging of lymph nodes in a spontaneous mouse prostate tumor model. *J Biomed Opt* 2011; **16**: 016004 [PMID: 21280910 DOI: 10.1117/1.3528027]
53 **van der Poel HG**, Buckle T, Brouwer OR, Valdés Olmos RA, van Leeuwen FW. Intraoperative laparoscopic fluorescence guidance to the sentinel lymph node in prostate cancer patients: clinical proof of concept of an integrated functional imaging approach using a multimodal tracer. *Eur Urol* 2011; **60**: 826-833 [PMID: 21458154 DOI: 10.1016/j.eururo.2011.03.024]
54 **Brouwer OR**, Buckle T, Vermeeren L, Klop WM, Balm AJ, van der Poel HG, van Rhijn BW, Horenblas S, Nieweg OE, van Leeuwen FW, Valdés Olmos RA. Comparing the hybrid fluorescent-radioactive tracer indocyanine green-99mTc-nanocolloid with 99mTc-nanocolloid for sentinel node identification: a validation study using lymphoscintigraphy and SPECT/CT. *J Nucl Med* 2012; **53**: 1034-1040 [PMID: 22645297 DOI: 10.2967/jnumed.112.103127]
55 **Brouwer OR**, van den Berg NS, Mathéron HM, van der Poel HG, van Rhijn BW, Bex A, van Tinteren H, Valdés Olmos RA, van Leeuwen FW, Horenblas S. A hybrid radioactive and fluorescent tracer for sentinel node biopsy in penile carcinoma as a potential replacement for blue dye. *Eur Urol* 2014; **65**: 600-609 [PMID: 24355132 DOI: 10.1016/j.eururo.2013.11.014]
56 **Jakobsen JK**, Alslev L, Ipsen P, Costa JC, Krarup KP, Sommer P, Nerstrøm H, Toft BG, Høyer S, Bouchelouche K, Jensen JB. DaPeCa-3: Promising Results of Sentinel Node Biopsy Combined with 18 F-FDG PET/CT in Clinically Lymph Node Negative Patients with Penile Cancer - a National Study from Denmark. *BJU Int* 2015; Epub ahead of print [DOI: 10.1111/bju.13243]
57 **You S**, Kang DK, Jung YS, An YS, Jeon GS, Kim TH. Evaluation of lymph node status after neoadjuvant chemotherapy in breast cancer patients: comparison of diagnostic performance of ultrasound, MRI and 18F-FDG PET/CT. *Br J Radiol* 2015; **88**: 20150143 [PMID: 26110204 DOI: 10.1259/bjr.20150143]
58 **Leijte JA**, Kroon BK, Valdés Olmos RA, Nieweg OE, Horenblas S. Reliability and safety of current dynamic sentinel node biopsy for penile carcinoma. *Eur Urol* 2007; **52**: 170-177 [PMID: 17316967 DOI: 10.1016/j.eururo.2007.01.107]
59 **Lam W**, Alnajjar HM, La-Touche S, Perry M, Sharma D, Corbishley C, Pilcher J, Heenan S, Watkin N. Dynamic sentinel lymph node biopsy in patients with invasive squamous cell carcinoma of the penis: a prospective study of the long-term outcome of 500 inguinal basins assessed at a single institution. *Eur Urol* 2013; **63**: 657-663 [PMID: 23153743 DOI: 10.1016/j.eururo.2012.10.035]
60 **Partin AW**, Kattan MW, Subong EN, Walsh PC, Wojno KJ, Oesterling JE, Scardino PT, Pearson JD. Combination of prostate-specific antigen, clinical stage, and Gleason score to predict pathological stage of localized prostate cancer. A multi-institutional update. *JAMA* 1997; **277**: 1445-1451 [PMID: 9145716 DOI: 10.1001/jama.277.18.1445]
61 **Briganti A**, Larcher A, Abdollah F, Capitanio U, Gallina A, Suardi N, Bianchi M, Sun M, Freschi M, Salonia A, Karakiewicz PI, Rigatti P, Montorsi F. Updated nomogram predicting lymph node invasion in patients with prostate cancer undergoing extended pelvic lymph node dissection: the essential importance of percentage of positive cores. *Eur Urol* 2012; **61**: 480-487 [PMID:

22078338 DOI: 10.1016/j.eururo.2011.10.044]
62 **Blute ML**, Leibovich BC, Cheville JC, Lohse CM, Zincke H. A protocol for performing extended lymph node dissection using primary tumor pathological features for patients treated with radical nephrectomy for clear cell renal cell carcinoma. *J Urol* 2004; **172**: 465-469 [PMID: 15247704]
63 **Hutterer GC**, Patard JJ, Perrotte P, Ionescu C, de La Taille A, Salomon L, Verhoest G, Tostain J, Cindolo L, Ficarra V, Artibani W, Schips L, Zigeuner R, Mulders PF, Valeri A, Chautard D, Descotes JL, Rambeaud JJ, Mejean A, Karakiewicz PI. Patients with renal cell carcinoma nodal metastases can be accurately identified: external validation of a new nomogram. *Int J Cancer* 2007; **121**: 2556-2561 [PMID: 17691107]
64 **Babaian KN**, Kim DY, Kenney PA, Wood CG, Wong J, Sanchez C, Fang JE, Gerber JA, Didic A, Wahab A, Golla V, Torres C, Tamboli P, Qiao W, Matin SF, Wood CG, Karam JA. Preoperative predictors of pathological lymph node metastasis in patients with renal cell carcinoma undergoing retroperitoneal lymph node dissection. *J Urol* 2015; **193**: 1101-1107 [PMID: 25390078 DOI: 10.1016/j.juro.2014.10.096]
65 **Langer I**, Guller U, Berclaz G, Koechli OR, Schaer G, Fehr MK, Hess T, Oertli D, Bronz L, Schnarwyler B, Wight E, Uehlinger U, Infanger E, Burger D, Zuber M. Morbidity of sentinel lymph node biopsy (SLN) alone versus SLN and completion axillary lymph node dissection after breast cancer surgery: a prospective Swiss multicenter study on 659 patients. *Ann Surg* 2007; **245**: 452-461 [PMID: 17435553 DOI: 10.1097/01.sla.0000245472.47748.ec]
66 **Kamprath S**, Possover M, Schneider A. Laparoscopic sentinel lymph node detection in patients with cervical cancer. *Am J Obstet Gynecol* 2000; **182**: 1648 [PMID: 10871497 DOI: 10.1067/mob.2000.104144]
67 **Corvin S**, Schilling D, Eichhorn K, Hundt I, Hennenlotter J, Anastasiadis AG, Kuczyk M, Bares R, Stenzl A. Laparoscopic sentinel lymph node dissection--a novel technique for the staging of prostate cancer. *Eur Urol* 2006; **49**: 280-285 [PMID: 16364536 DOI: 10.1016/j.eururo.2005.08.021]
68 **Rossi EC**, Ivanova A, Boggess JF. Robotically assisted fluorescence-guided lymph node mapping with ICG for gynecologic malignancies: a feasibility study. *Gynecol Oncol* 2012; **124**: 78-82 [PMID: 21996262 DOI: 10.1016/j.ygyno.2011.09.025]
69 **ElSahwi KS**, Hooper C, De Leon MC, Gallo TN, Ratner E, Silasi DA, Santin AD, Schwartz PE, Rutherford TJ, Azodi M. Comparison between 155 cases of robotic vs. 150 cases of open surgical staging for endometrial cancer. *Gynecol Oncol* 2012; **124**: 260-264 [PMID: 22036203 DOI: 10.1016/j.ygyno.2011.09.038]

P- Reviewer: Bahlmann F, Marickar YMF **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Lu YJ

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com