Leili Zarifmahmoudi^a
Hamidreza Ghorbani^b
Kayvan Sadri^a
Mahmoud Tavakkoli^b
Maliheh Keshvari^b
Maryam Salehi^c
Ramin Sadeghi^a

^aNuclear Medicine Research Center, Mashhad University of Medical Sciences, Mashhad, Iran; ^bKidney Transplantation Complications Research Center, Mashhad University of Medical Sciences, Mashhad, Iran; ^cDepartment of Community Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

Sentinel Node Biopsy in Urothelial Carcinoma of the Bladder: Systematic Review and Meta-Analysis

Keywords

Bladder · Cancer · Sentinel lymph node

Abstract

Objectives: To determine the application of sentinel node biopsy in urothelial carcinoma of the bladder, we performed a systematic review and meta-analysis. **Methods:** Pooled false negative rate and detection rate were presented using Meta-Disc (version 1.4), and comprehensive meta-analysis (version 2). Publication bias and heterogeneity were assessed using funnel plot, Cochrane Q test, and I^2 index. **Results:** The pooled detection rate was 91% (95% CI 87–93%) and pooled sensitivity was 79% (95% CI 0.69–0.86%). When the neoadjuvant chemotherapy group of patients was omitted, the pooled sensitivity changed to 82% (95% CI 74–88%), and the Cochrane Q and I^2 statistics were 15.44 and 48.2%, respectively. The pooled sensitivity of studies that included >50% of pT 3 or 4 patients was 70% (59–80), by omitting studies that enrolled >50% of patients at pT stage of 3 or 4, the pooled sensitivity increased to 93% (81–98). **Conclusions:** Although the studies on SN biopsy of muscle invasive bladder cancer patients resulted in a high detection rate and sensitivity, further validated multicenter trials with larger sample size are essential to confirm the reliability and accuracy of this approach and obtain a standardized method. We

showed that pT1 or pT2 bladder cancer patients with clinically negative lymph nodes are the most appropriated group for sentinel lymph node mapping.

© 2019 S. Karger AG, Basel

Introduction

Muscle invasive bladder cancer (MIBC) is among the most commonly diagnosed cancers worldwide leading to significant morbidity and mortality mostly within 2 years of diagnosis [1]. Despite various new technologies, radical cystectomy (RC) is performed as the gold standard treatment option and pelvic lymph node dissection (PLND) as an integral part of the surgical management of bladder cancer patients. Although PLND is routinely performed for MIBC patients during RC, its beneficial effects on survival and recurrence rate remain unknown [2, 3].

Due to long operative time, costs, and adverse effects associated with regional lymphadenectomy in bladder cancer patients, sentinel lymph node (SLN) biopsy (SLNB) might be regarded as a better approach in guiding lymph node dissection, similar to breast and melanoma tumors. SLN mapping is a simple and a less-invasive technique with minimal side effects compared with LND, which is first applied in penile cancer by Cabanas [4].

The pattern of lymph fluid drainage is specific in each and the sentinel node as the first lymph node along the lymphatic vessels receives the lymph fluid and malignant cells from the primary tumor and act as the primary gateway for spreading cancerous cells to distal organs. So, SLNs can reflect the pathologic status of the remaining lymphatic region in a less extensive surgical procedure and potentially can improve LN staging by identifying the metastases in patients with no clinical evidence of LN involvement [5].

The importance of sentinel node biopsy in therapeutic decision making for patients was first determined in melanoma and then established in breast cancers [6]. The application of SLNB has been extended to other malignancies including gynecological, and gastrointestinal cancers too [7–11].

So far several studies have been performed on the sentinel node biopsy in MIBC. To investigate the diagnostic value of SLND in MIBC patients, we performed this systematic review and meta-analysis based on the currently available literature.

Method

This systematic review was conducted based on the preferred reporting items for systematic reviews and meta-analyses guidelines and checklist [12]. The protocol of this systematic review and meta-analysis is based on the thesis that has been approved in Mashhad University of Medical Sciences with the number 940295.

Literature Search

A comprehensive search on PubMed and Scopus was done to identify the relevant published articles in sentinel node mapping of invasive bladder cancer from inception to April 2018. The searched keywords were as follows: “sentinel AND bladder”; no language or date limitation was applied for the search strategy. The reference list of selected articles was also hand searched to prevent missing any relevant articles. The authors of included articles were contacted if additional information were needed.

Inclusion and Exclusion Criteria

Inclusion criteria were as follows: (a) all the clinical and original articles analyzing effectiveness, importance, and outcome of SLN mapping in clinically node negative patients with invasive bladder cancer; (b) those that reported accurate data regarding SNs detection rate and false negative rate.

Duplicated articles were omitted by selecting the article with a larger sample size. Articles without accurate data on intraoperative SNs identification using a gamma probe were excluded.

Data Extraction

Data were extracted independently by 2 authors from original articles based on a set of predefined parameters, including authors, publication year, number of cases, age, sex, stage of the tumor,

substance used for lymph node identification, method of mapping, type of surgery, mean number of identified lymph nodes, pathological evaluation of both sentinel and resected lymph nodes, global detection rate, and sensitivity.

Quality Assessments

The methodological quality of the eligible included articles was assessed according to the established quality rating critical appraisal tool obtained from 2016 Oxford Centre for Evidence-Based Medicine and the Cochrane Collaboration's tool for assessing risk of bias for diagnostic studies [13].

Statistics

The pooled sensitivity and detection rate of SLNB technique were calculated based on the results of each study and using the random-effects model [14]. Heterogeneity was evaluated based on Cochrane Q test (p value less than 0.05 was considered statistically significant) and I^2 index statistics. The funnel plot was used to show the possible publication bias based on the asymmetry of the plot. Meta-Disc (version 1.4) [15] and comprehensive meta-analysis (version 2) were used for statistical analyses.

Results

Study Selection

The selection process of the included articles is summarized according to preferred reporting items for systematic reviews and meta-analyses flowchart (Fig. 1).

The initial electronic search of the above-mentioned search strategy resulted in 281 potentially relevant studies in PubMed and Scopus, regarding the SLNB in bladder cancer. Following reviewing the titles and abstracts, 254 were omitted out of the initially yielded articles, and 27 abstracts were related to the purpose of this study; however, 20 were excluded following studying the full text due to unrelated methodology or not reporting the mentioned including criteria in the result part. Duplicate studies were omitted in the next step by selecting the study with a larger sample size. One reference was added after reviewing the reference list of the extracted items. Eventually, 8 articles were included as the most related to the inclusion criteria of this systematic review in the final analysis [16–23].

All studies were cross-sectional studies that explored the diagnostic value of SLNB in the bladder cancer. The characteristics of the 8 included articles as well as the quality assessment results were extracted and presented in Tables 1 and 2, respectively.

Studies Characteristics

Three hundred thirty-six patients (106 female, 230 male) with MIBC at clinical stage of cT1-T4N0M0 diagnosed by MRI or CT and candidate for cystectomy and

Fig. 1. Preferred reporting items for systematic reviews and meta-analyses flowchart of the study inclusion process.

pelvic lymphadenectomy were studied in 8 eligible included articles [16–23].

There was no significant difference regarding the included patients characteristics in 7 [16–20, 22, 23] of the selected articles; patients would be excluded from the studies if they were found to have non-urothelial cancer, multifocal tumors or carcinoma in situ, primary pelvic radiotherapy, procedures in the pelvis, advanced tumor stage, non-MIBC, or any previous radiotherapy.

The study of Rosenblatt et al. [21] contained information about the one who performed SLNB on MIBC patients with the history of neoadjuvant chemotherapy (NAC) to determine the feasibility of SLNB in all pT stages. The study of Aljabery et al. [16] contained the largest sample size (103 cases). However, the study of Sherif et al. [23] was the one with the smallest sample size (6 cases) among the included studies.

The injection site was reported differently in these 8 studies including the submucosa of the bladder [18, 20, 22] or into the detrusor muscle [16–19, 21, 23], around the visible tumor or tumor margin.

Detection Rate

The forest plot obtained based on the detection rate of the 8 included studies on MIBC patients with or without previous chemotherapy showed the graphical representation of the detection rate (Fig. 2). The pooled detection rate for all the applied techniques of SNs mapping was 91% (95% CI 87–93%). Following evaluating the heterogeneity, Cochrane Q value was 7.78 ($p = 0.6$), and the I^2 index was 0%. Funnel plot of the pooled detection rate is shown in Figure 3. The Egger's regression intercept was 0.18 ($p = 0.8$) as the statistical evaluation of the asymmetry of the funnel plot.

By omitting patients with previous chemotherapy included in the study of Rosenblatt et al. [21] (47 patients out of 338), the pooled detection rate did not change significantly: 91% (95% CI 87–93%).

By evaluating 3 studies that applied blue dye for SNs mapping, the pooled detection rate was 21% (95% CI 0.02–0.75) [17, 22, 23].

Pooling 2 studies that applied indocyanine green (ICG) for SNs mapping showed the detection rate of 93% (95% CI 83–97%) [18, 20].

Sensitivity

A forest plot of the pooled sensitivity is presented in Figure 4. By considering all NAC and no NAC patients, pooled sensitivity was 79%, (95% CI 0.69–0.86%), estimated heterogeneity showed the Cochrane Q value as 23.63 ($p = 0.0001$) and the I^2 index as 66.2%. However, when the NAC group of patients was omitted, the pooled sensitivity changed to 82% (95% CI 74–88%), and the Cochrane Q and I^2 statistics were 15.44 and 48.2%, respectively.

Subgroup analysis based on the number of pT3 and pT4 patients showed pooled sensitivity of 70% (59–80), and 93% (81–98) for studies with >50%, and <50% of recruited patients with pT3 and pT4 tumors.

Quality and Risk Bias Assessment

Several types of biases might occur in different parts of each diagnostic study including patients (the selection bias, spectrum bias), index test (information bias), reference test (misclassification bias and partial verification bias), disease/condition progression bias (perform the reference and index with minimal delay), and differential verification bias [24]. All the mentioned risk of biases have been evaluated following quality assessment of the current systematic review and meta-analysis according to the 2016 Oxford Centre for Evidence-Based Medicine and the Cochrane Collaboration's tool for assessing the risk of bias for diagnostic studies (Table 2; Fig. 5, 6) [13].

Table 1. Characteristics of the included articles

Author, reference number, year, country	Participant characteristics	Technique of sentinel node mapping	Time of radiotracer injection	Patients with at least one detected inguinal sentinel nodes/total number of patient	False negative rate	True positive	SLN drainage	Localization of metastatic SLN
Sherif et al. [22], 2001, Sweden	Number: 13 pT1: 3 pT2: 4 pT3: 3 pT4: 3 Mean age: 62.6 years Gender: 2 F/11 M	Preoperative lymphoscintigraphy Intraoperative γ -probing and blue dye	Before the surgery and repeated If >24 h had a single lapse since the latter	11/12	0	4	NR	
Marits et al. [19], 2006, Sweden	Number: 14 pT1: 1 pT2: 12 pT3: 1 Mean age: 65.4 years Gender: 3 F/11 M	Preoperative lymphoscintigraphy and SPECT Intraoperative blue dye and γ -probing	On the same day	12/14	0	7	NR	
Sherif et al. [23], 2006, Sweden	Number: 6 pT1: 1 pT2: 5 Mean age: 69.5 years Gender: 2 F/4 M	Preoperative lymphoscintigraphy and SPECT Intraoperative blue dye and γ -probing	Before the surgery and repeated If >24 h had a single lapse since the latter	5/6	0	2	5/6 with bilateral distribution	Obturator fossa, outside the obturator region, common, internal, and external iliac
Liedberg et al. [17], 2006, Sweden	Number: 75 pT0: 6 pTa: 3 pTCIS: 2 pT1: 3 pT2: 19 pT3: 37 pT4: 5 Mean age: 65 years Gender: 16 F/59 M	Preoperative lymphoscintigraphy Intraoperative γ -probing and blue dye	1–4 days before surgery and on the day of surgery	65/75	6	26	NR	Only outside obturator fossa: common, internal, and external iliac, perivesical and vesicovaginal septum
Polom et al. [20], 2017, Poland	Number: 50 Mean age: 65 years Gender: 12 F/38 M	Hybrid SPECT/CT lymphoscintigraphy Intraoperative γ -probing Intraoperative injection of ICG	RadCol: day before surgery ICG: just before surgery	RadCOL 47/50 ICG 47/50	RadCOL 1 ICG 2	RadCOL 15 ICG 16	9/38 with contralateral lymphatic outflow	Proximal, distal, and caudal to the uretero-iliac crossing
Aljabery et al. [16], 2017, Sweden	Number: 103 pT1: 12 pT2: 20 pT3: 48 pT4: 23 Mean age: 69 years Gender: 23 F/80 M	Intraoperative γ -probing and blue dye	Just before surgery	83/103	13	20	NR	NR
Manny and Hemal [18], 2014, US	Number: 10 pT0: 1 pT1: 3 pT2: 1 pT4: 5 Median age: 71 years (range 54–77 years) Gender: 4 F/6 M	Intraoperative injection of ICG	Just before surgery	9/10	0	2	8/9 with bilateral SLN drainage	Right and left obturator, right external iliac
Rosenblatt et al. [21], 2017, Sweden	Number: 65 NACDOWN: 24 NACnodown: 23 No-NAC: 18 pT2: 44 pT3: 20 pT4: 1 Mean age: 69.1 Gender: 18 F/47 M	Intraoperative γ -probing	Just before surgery	NACDOWN 22/24 NACnodown 21/23 NONAC 17/18	NACDOWN and NACnodown 5 NO-NAC 0	NACDOWN and NACnodown 1 NO-NAC 2	NR	NR

SPECT, single-photon emission computed tomography; ICG, indocyanine green; RadCol, radiocolloid; NAC, neoadjuvant chemotherapy; NACDOWN, patients who received NAC and completely downstaged; SNL, sentinel lymph node; NR, not reported.

Table 2. Quality and bias assessment of the included studies

Author, reference number, year	The spectrum of the patients; patients were selected regardless of the T stage (spectrum bias)	Consecutive recruitment (selection bias)	Gold standard (misclassification bias)	Independent, blind comparison between the index test and an appropriate reference ("gold") standard of diagnosis (information bias)	Application of gold standard to all patients regardless of SLN results (partial verification and differential verification biases)
Sherif et al. [22], 2001	Yes	Consecutive	Radical cystectomy extended lymphadenectomy	NR	Yes
Marits et al. [19], 2006	Yes	Consecutive	Radical cystectomy extended lymphadenectomy	NR	Yes
Sherif et al. [23], 2006	No	Consecutive	Radical cystectomy extended lymphadenectomy	NR	Yes
Liedberg et al. [17], 2006	Yes	Consecutive	Radical cystectomy extended lymphadenectomy	NR	Yes
Polom et al. [20], 2017	NA	Consecutive	Radical cystectomy extended lymphadenectomy	NR	Yes
Aljabery et al. [16], 2015	Yes	Consecutive	Radical cystectomy extended lymphadenectomy	NR	Yes
Manny and Hemal [18], 2014	Yes	Consecutive	Radical cystectomy extended lymphadenectomy	NR	Yes
Rosenblatt et al. [21], 2016	Yes	Consecutive	Radical cystectomy extended lymphadenectomy	NR	Yes

SLN, sentinel lymph node; NR, not reported.

Fig. 2. Forest plot of the detection rate.

Discussion

Extended PLND with RC is a treatment option performed routinely for patients with MIBC. However, there are controversies regarding the extent of lymph nodes dissection [25]. It has been shown that LNs involvement and unrecognized metastasis might be present in almost one-third of MIBC patients, which is detected by the resection of LNs; so, bilateral PLND is suggested to be associated routinely with cystectomy even for CN0 MIBC patients [2].

Regarding the importance of lymph node status in revealing the disease prognosis and planning the future treatment, NCCN guideline and NCCN bladder panel recommendations suggested performing PLND alongside the surgery as an integral part of the surgical management, which might increase the survival rate and lower pelvic recurrence; this is due to low sensitivity of staging invisible bladder cancer through cystectomy and TURBT and inability of CT and MRI in revealing the presence of micrometastasis [26].

Fig. 3. Funnel plot of the detection rate.

Fig. 4. Forest plot of the sensitivity.

Fig. 5. Risk of bias graph: Author's judgments of risk of bias presented as percentages across all included studies.

Sentinel node mapping has been evaluated for the diagnosis of pelvic lymph node involvement in MIBC in several studies. Our study was done to systematically review the available literature on the importance of SLND in MIBC patients.

False Negative and Detection Rate

The pooled detection rate of the included studies was high (90% [95% CI 85.2–93.3%]), and this shows that finding at least one sentinel node in bladder cancer patients is feasible intra-operatively.

	Risk of bias				Applicability concerns		
	Patient selection	Index text	Reference standard	Flow and timing	Patient selection	Index text	Reference standard
Aljabery, 2015	+	+	?	+	?	+	+
Liedberg, 2006	+	+	+	+	+	+	+
Manny, 2014	+	+	+	+	+	+	+
Marits, 2005	+	+	+	+	+	+	+
Polom, 2016	+	+	+	+	+	+	+
Rosenblatt, 2016	+	+	+	+	+	+	+
Sherif, 2001	+	+	+	+	+	+	+
Sherif, 2006	+	+	+	?	+	+	+

High
 Unclear
 Low

Fig. 6. Risk of bias summary: systematic review. Author's judgments of risk of bias item for each included study.

The false negative rate is the single most important index of diagnostic performance in sentinel node biopsy. Based on the current meta-analysis, SLN biopsy had a pooled sensitivity of 79%, (95% CI 0.69–0.86%). Different possible reasons may increase the FN rate, such as technical issues in injection of the tracers, obstruction of lymph flow of tracer to SNs due to metastatic involvement of the SNs and detection of another node instead of the main SNs, and SN detection in one side despite the SNs involvement on the contralateral side [17, 27, 28]. We explored different variables that could affect the detection rate and sensitivity.

pT Stage of MIBC Patients

All the studies included patients with the different pT stage of MIBC (T0–T4), which might affect the obtained FN rate and sensitivity of the procedure. Fifty percent or more of the patients of 5 of the included studies were at pT stage of 3 or 4 [9, 16–18, 21]. The study of Aljabery et al. [16] included 71 out of 103 (69%) patients at PT3–PT4 with non-organ confined tumors, which might be the reason of the

high FN rate. Based on the meta-analysis, sensitivity would decrease to 70% while including patients at pT stage of 3 or 4; however, sensitivity would increase to 93% by omitting patients with higher stages of the disease. Therefore, SLN mapping has shown the most accuracy in MIBC patients with lower pT stages. This result is also in accordance with sentinel node mapping in other tumors [29–33].

Technique

The inconsistency of the SLN biopsy approach was related to the injection site, detecting technique, and applied tracers (radioactive agent, dye, and ICG).

Heterogeneity regarding the radioactive tracer for detecting the SNs was due to the radiolabelled nanocolloid particles, which were similar in composition but different in size; technetium radiocolloid (radioactive tracer Nanocol or Albures) was used in 7 of the studies for preoperative detecting techniques including planar lymphoscintigraphy [17, 19, 22, 23] and SPECT/CT [19, 20, 23], or intraoperative SNs detection using handheld γ -detecting probe [16, 17, 19–23].

Five out of 8 included studies applied the intraoperative blue dye detection technique [16, 17, 19, 22, 23] and utilized 1 mL patent blue dye peritumorally into detrusor muscle for SLN detection, but only 3 of them reported the data related to the blue dye detection rate [17, 22, 23]. According to these reports, applying dye is easy and cost effective, and nodes and lymphatic channels containing blue dye could be observed visually intraoperatively; however, blue dye application was associated with a low detection rate of SLNs compared to radiotracers, which might be due to the short time interval between the injection of blue dye and performance of nodal mapping [17], which is also in accordance with the previous studies of sentinel node mapping in other tumors [34–37]. This was also evident in our meta-analysis based on these 3 studies used blue dye.

Only 2 studies applied fluorescence-enhanced robotic RC and ICG lymphangiography using a cystoscopic injection of ICG, which proposed this technique as reliable and suitable. Although we obtained a high detection rate in our meta-analysis of these 2 studies, these results cannot be generalizable due to a low number of studies performed with this technique and their low sample size, so more studies are needed in this regard [18, 20].

Injection Time

In order to perform lymphoscintigraphy, radiotracer was injected before the major surgery in several studies; however, if more than 24 h had passed following lympho-

scintigraphy, the injection would be repeated again on the day of surgery [16, 17, 19–23]. Studies that used blue dye, all injected the dye at the time of surgery [16, 17, 19, 22, 23]. Regarding the NIFR technique, ICG was injected before the main surgery and identification of SLNs was achieved almost 30 min following the injection of ICG [18, 20]. Overall, the time of tracer injection does not seem to be related to the success of sentinel node mapping.

Lymphatic Drainage

Pelvic has a complex lymphatic pattern, and bladder sentinel drainage is very variable with different localization in patients, which can be bilateral or unilateral. The bilateral distribution of SLNs independent of the tumor position, named as the Crossover phenomena, might be due to simultaneous SNs initiating from different parts of tumors and anatomically different lymphatic routes in individuals. Despite the lateralized bladder tumor, various patients have shown contralateral involvement of the nodes in previous reports [38]. Bilateral distribution was reported in 4 of the included studies. [16, 18, 20, 23], which were mainly detected through the hybrid SPECT/CT technique in 5 out of 6 patients, of which 2 had metastatic SNs in non-obturator localizations [23], ICG lymphangiography [18] in 8 out of 9 patients, and intraoperative SLNs mapping [16] in 30% of the patients. Overall, the reported results regarding the bilateral distribution of the SNs confirm the necessity of the bilateral lymph node dissection following RC.

In penile, endometrial, and vulvar cancers, as the mid-line tumors, unilateral inguinal lymph node drainage increases the possibility of inguinal lymph node involvement on the side without drainage [39]. Unilateral SNs detection might lead to an increased the false negative rate because of the contralateral involvement of SNs, so further evaluations are needed to clarify this issue in the bladder cancer.

According to the included studies, the majority of SLNs will be found around the bladder, distally and caudally to the uretero iliac crossing; however, SLN mapping could reveal metastatic or non-metastatic SLNs located outside the obturator region, including internal, external, and common iliac lymph nodes, or outside the PLND template (above aortic bifurcation) [17, 18, 22, 23, 40]. The existence of metastatic SLNs outside the obturator fossa improves the overall staging accuracy even beyond extended bilateral PLND dissection, which is not limited only to the obturator fossa.

Lymphadenectomy

Extended pelvic lymphadenectomy by bilateral dissection of the sentinel nodes and non sentinel nodes of the obturator region along iliac vessels (internal, external, and common) with a preperitoneal approach and dissection up to the aortic bifurcation was performed in all the studies.

Publication Bias

Publication bias is evaluated graphically based on the funnel plot. According to the symmetry of the Funnel plot, no important publication bias existed.

Quality and Bias Assessment

According to the Table 2, Figures 5 and 6, the quality of the included studies was acceptable and no important biases could be detected.

In conclusion, although the studies on SN biopsy of MIBC patients resulted in high sensitivity of this technique, further validated multicenter trials with a larger sample size are essential to confirm the reliability and accuracy of this approach and obtaining a standardized method. Based on the existing studies, pT1 or pT2 bladder cancer patients with clinically negative lymph nodes are the most appropriated group for SLN mapping.

Disclosure Statement

The authors declare that they have no conflicts of interest to disclose.

Funding Source

This study was supported by vice chancellor of research of Mashhad University of Medical Sciences with the approval number of 940295.

Authors Contribution

L.Z. and R.S.: conception or design of the work, acquisition, analysis, or interpretation of data, drafting the work or revising. H.G.: conception or design of the work, drafting the work or revising, acquisition of data. K.S., M.T., M.K., and M.S.: conception or design of the work, drafting the work or revising, interpretation of data.

References

- Burger M, Catto JW, Dalbagni G, Grossman HB, Herr H, Karakiewicz P, et al. Epidemiology and risk factors of urothelial bladder cancer. *Eur Urol*. 2013 Feb;63(2):234–41.
- Network NCC. NCCN guidelines. 2015.
- Karl A, Carroll PR, Gschwend JE, Knüchel R, Montorsi F, Stief CG, et al. The impact of lymphadenectomy and lymph node metastasis on the outcomes of radical cystectomy for bladder cancer. *Eur Urol*. 2009 Apr;55(4):826–35.
- Cabanas RM. An approach for the treatment of penile carcinoma. *Cancer*. 1977 Feb;39(2):456–66.
- Ji RC. Lymph Nodes and Cancer Metastasis: New Perspectives on the Role of Intranasal Lymphatic Sinuses. *Int J Mol Sci*. 2016 Dec;18(1):51.
- Morton DL, Thompson JF, Cochran AJ, Mozzillo N, Nieweg OE, Roses DF, et al.; MSLT Group. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. *N Engl J Med*. 2014 Feb;370(7):599–609.
- Ansari M, Rad MA, Hassanzadeh M, Gholami H, Yousefi Z, Dabbagh VR, et al. Sentinel node biopsy in endometrial cancer: systematic review and meta-analysis of the literature. *Eur J Gynaecol Oncol*. 2013;34(5):387–401.
- Javan H, Gholami H, Assadi M, Pakdel AF, Sadeghi R, Keshtgar M. The accuracy of sentinel node biopsy in breast cancer patients with the history of previous surgical biopsy of the primary lesion: systematic review and meta-analysis of the literature. *Eur J Surg Oncol*. 2012 Feb;38(2):95–109.
- Sadeghi R, Gholami H, Zakavi SR, Kakhki VR, Tabasi KT, Horenblas S. Accuracy of sentinel lymph node biopsy for inguinal lymph node staging of penile squamous cell carcinoma: systematic review and meta-analysis of the literature. *J Urol*. 2012 Jan;187(1):25–31.
- Tehrani S, Treglia G, Krag DN, Dabbagh Kakhki VR, Zakavi SR, Sadeghi R, et al. Sentinel node mapping in anal canal cancer: systematic review and meta-analysis. *J Gastrointest Liver Dis*. 2013 Sep;22(3):321–8.
- Wong SL, Balch CM, Hurley P, Agarwala SS, Akhurst TJ, Cochran A, et al.; American Society of Clinical Oncology; Society of Surgical Oncology. Sentinel lymph node biopsy for melanoma: American Society of Clinical Oncology and Society of Surgical Oncology joint clinical practice guideline. *J Clin Oncol*. 2012 Aug;30(23):2912–8.
- Sadeghi R, Treglia G. Systematic reviews and meta-analyses of diagnostic studies: a practical guideline. *Clin Transl Imaging*. 2017;5(2):83–7.
- Oxford Centre for Evidence-Based Medicine: Levels of Evidence.
- DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986 Sep;7(3):177–88.
- Zamora J, Abraira V, Muriel A, Khan K, Coomarasamy A. Meta-DiSc: a software for meta-analysis of test accuracy data. *BMC Med Res Methodol*. 2006 Jul;6(1):31.
- Aljabery F, Shabo I, Olsson H, Gimm O, Jahnson S. Radio-guided sentinel lymph node detection and lymph node mapping in invasive urinary bladder cancer: a prospective clinical study. *BJU Int*. 2017 Sep;120(3):329–36.
- Liedberg F, Chebil G, Davidsson T, Gudjonsson S, Månsson W. Intraoperative sentinel node detection improves nodal staging in invasive bladder cancer. *J Urol*. 2006 Jan;175(1):84–8.
- 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 Apr;83(4):824–9.
- Marits P, Karlsson M, Sherif A, Garske U, Thörn M, Winqvist O. Detection of immune responses against urinary bladder cancer in sentinel lymph nodes. *Eur Urol*. 2006 Jan;49(1):59–70.
- Polom W, Markuszewski M, Cytawa W, Czapiewski P, Lass P, Matuszewski M. Fluorescent Versus Radioguided Lymph Node Mapping in Bladder Cancer. *Clin Genitourin Cancer*. 2017 Jun;15(3):e405–9.
- Rosenblatt R, Johansson M, Alamdari F, Sidiqi A, Holmström B, Hansson J, et al. Sentinel node detection in muscle-invasive urothelial bladder cancer is feasible after neoadjuvant chemotherapy in all pT stages, a prospective multicenter report. *World J Urol*. 2017 Jun;35(6):921–7.
- 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 Sep;166(3):812–5.
- 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 Jul;50(1):83–91.
- Roever L. Types of Bias in Studies of Diagnostic Test Accuracy. *Evidence Based Medicine and Practice Open Access Journal*. 2015;10:2.
- Youssef RF, Raj GV. Lymphadenectomy in management of invasive bladder cancer. *Int J Surg Oncol*. 2011;2011(Jun):758189.
- Paik ML, Scolieri MJ, Brown SL, Spirnak JP, Resnick MI. Limitations of computerized tomography in staging invasive bladder cancer before radical cystectomy. *J Urol*. 2000 Jun;163(6):1693–6.
- 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*. 2013 May-Jun;7(5-6):E322–8.
- Sadeghi R, Hassanzadeh M. Sentinel lymph node biopsy algorithm: can it be a universal method for midline tumors? *Gynecol Oncol*. 2014 Feb;132(2):273–4.
- Assadi M, Yarani M, Zakavi SR, Jangjoo A, Memar B, Treglia G, et al. Sentinel node mapping in papillary thyroid carcinoma using combined radiotracer and blue dye methods. *Endokrynol Pol*. 2014;65(4):281–6.
- Hassanzadeh M, Hosseini Farahabadi E, Yousefi Z, Kadkhodayan S, Zarifmohamudi L, Sadeghi R. Lymphatic mapping and sentinel node biopsy in ovarian tumors: a study using intra-operative Tc-99m-Phytate and lymphoscintigraphy imaging. *J Ovarian Res*. 2016 Sep;9(1):55.
- Zarifmohamudi L, Sadeghi R. Reliability of the sentinel node mapping according to time from surgery in breast cancer patients with previous excisional biopsy: comment on Sabaté-Llobera et al. study. *Rev Esp Med Nucl Imagen Mol*. 2015 May-Jun;34(3):217.
- Khadivi E, Daghighi M, Khazaeni K, Dabbagh Kakhki VR, Zarifmohamudi L, Sadeghi R. Intra-Operative Lymphatic Mapping and Sentinel Node Biopsy in Laryngeal Carcinoma: preliminary Results. *Iran J Otorhinolaryngol*. 2015 Jul;27(81):285–91.
- Dabbagh Kakhki VR, Bagheri R, Tehranian S, Shojaei P, Gholami H, Sadeghi R, et al. Accuracy of sentinel node biopsy in esophageal carcinoma: a systematic review and meta-analysis of the pertinent literature. *Surg Today*. 2014 Apr;44(4):607–19.
- Bagheri R, Naghavi F, Kakhki VR, Zakavi SR, Fattahi AS, Jafarian AH, et al. Sentinel node mapping in esophageal squamous cell carcinoma using intra-operative combined blue dye and radiotracer techniques. *Esophagus*. 2013 Dec;10(4):211–6.
- Fattahi AS, Tavassoli A, Rohbakhshfar O, Sadeghi R, Abdollahi A, Forghani MN. Can methylene blue dye be used as an alternative to patent blue dye to find the sentinel lymph node in breast cancer surgery? *J Res Med Sci*. 2014 Oct;19(10):918–22.
- Kadkhodayan S, Shiravani Z, Hassanzadeh M, Sharifi N, Yousefi Z, Fattahi A, et al. Lymphatic mapping and sentinel node biopsy in endometrial cancer—a feasibility study using cervical injection of radiotracer and blue dye. *Nucl Med Rev Cent East Eur*. 2014;17(2):55–8.
- Sadeghi R, Alesheikh G, Zakavi SR, Fattahi A, Abdollahi A, Assadi M, et al. Added value of blue dye injection in sentinel node biopsy of breast cancer patients: do all patients need blue dye? *Int J Surg*. 2014;12(4):325–8.

- 38 Mills RD, Turner WH, Fleischmann A, Markwalder R, Thalmann GN, Studer UE. Pelvic lymph node metastases from bladder cancer: outcome in 83 patients after radical cystectomy and pelvic lymphadenectomy. *J Urol*. 2001 Jul;166(1):19–23.
- 39 Esplugas S, Bila DM, Krause LG, Dezotti M. Ozonation and advanced oxidation technologies to remove endocrine disrupting chemicals (EDCs) and pharmaceuticals and personal care products (PPCPs) in water effluents. *J Hazard Mater*. 2007 Nov;149(3):631–42.
- 40 Połom W, Markuszewski M, Cytawa W, Lass P, Matuszewski M. Radio-Guided Lymph Node Mapping in Bladder Cancer Using SPECT/CT and Intraoperative γ -Probe Methods. *Clin Nucl Med*. 2016 Aug; 41(8):e362–7.