Feasibility of sentinel lymph node mapping in renal cell carcinoma using intraoperative radiotracer injection

Original Article

Leili Zarifmahmoudi[1], Hamidreza Ghorbani[2], Ramin Sadeghi[1], Kayvan Sadri[1], Salman Soltani[2], Atena Aghaee[1]

[1]Nuclear Medicine Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
[2]Kidney Transplantation Complications Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

(Received 31 January 2021, Revised 20 June 2021, Accepted 24 June 2021)

ABSTRACT

Introduction: The applicability of sentinel lymph node biopsy for early detection of metastasis in patients with renal cell carcinoma (RCC) is still in the validation phase and under investigation, which might be due to the unpredictability of the lymphatic pattern in RCC. In this study, we aimed to evaluate the feasibility and accuracy of sentinel node biopsy in patients with renal masses.

Methods: In this prospective study, twenty-one candidates for open radical nephrectomy with T1-T3 renal tumors, were included consecutively. Sentinel nodes were sought using a hand-held gamma probe following the injection of radiotracer. The validity of sentinel node biopsy procedure as our index test was compared with lymphadenectomy as the standard method for staging and detecting the regional lymph nodes metastasis.

Results: At least one sentinel lymph node was detected in thirteen of the patients using a hand-held gamma probe, and the detection rate was 61%. There was no patient with positive pathological involvement of the regional lymph nodes despite the negative involvement of the sentinel lymph node; so, the false-negative rate was 0%.

Conclusion: Although sentinel lymph node biopsy was feasible in patients with RCC, sentinel node detection failure was high in our study. More prospective studies with a larger sample size are needed for standardization of the radiotracer injecting aspects and mapping method to increase the detection rate and to evaluate the false negative rate more accurately.

Key words: Renal cell carcinoma; Sentinel lymph node; Nuclear medicine; Lymphoscintigraphy

Iran J Nucl Med 2021;29(2):73-78
Published: July, 2021
http://irjnm.tums.ac.ir

Corresponding author: Dr. Hamidreza Ghorbani, Kidney Transplantation Complications Research Center, Mashhad University of Medical Sciences, Mashhad, Iran. E-mail: ghorbanihr@mums.ac.ir

INTRODUCTION

Lymph node staging by lymph node dissection is the primary prognostic indicator of many solid tumors that can determine the ideal therapeutic strategy in various cancers. The role of lymph node dissection in surgical management of renal cell carcinoma (RCC) is controversial and still under debate in many aspects [1].

Conventional imaging techniques are used to evaluate the lymph nodes metastasis in RCC patients; even though, they are not precise enough to detect the small involved nodes or subclinical metastases [2]. The prevalence of lymph node metastasis at diagnosis of RCC has been decreased, and the pathological involvement of the regional lymph nodes is associated with poor prognosis. Due to the improvement of imaging techniques, including ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI), RCCs are diagnosed at earlier stage with smaller tumor size; however, the risk of lymphatic metastasis, especially in normal sized lymph nodes is still present.

Sentinel lymph node biopsy as an alternative staging approach resulted in less invasive and selective lymphadenectomy and significant advancements in lymph node staging, which was coined by Cabanas firstly in 1977 [3]. In this technique, the sentinel node is the first lymph node that receives the metastasis prior to other regional lymph nodes. Radioactive agent injected near the primary tumor will be transported to sentinel node; the detection and pathological assessment of the sentinel node lead to intraoperative regional lymph node assessment with comparable accuracy to extended lymphadenectomy in different cancers [4]. Compared with lymphadenectomy, this technique has shown lower comorbidities, aggressiveness, and more precise prognostic value in breast, melanoma, gynecological and gastrointestinal tumors [5-10].

Although uncertainty regarding the need for Lymph node dissection still exists for patients with RCC and the role of lymphadenectomy is contentious, lymph node dissection is recommended as the most reliable method for nodal staging in RCC [11, 12]. In patients with renal carcinoma, lymph node staging is performed through retroperitoneal lymphadenectomy of suspicious and enlarged lymph nodes following the radical nephrectomy [13]. The development of more accurate nodal staging tools lead to better evaluation of disease prognosis, and the patient might benefit from removal of pathologic lesions and cancer control [14].

Despite types of research, the applicability of sentinel node biopsy for early detection of metastasis in patients with RCC is still in the validation phase and under investigation, which might be due to the unpredictability of the lymphatic pattern in RCC.

In this study, we aimed to evaluate the feasibility and accuracy of sentinel lymph node biopsy in patients with RCC.

METHODS

In this prospective study, all patients with diagnosed RCC, candidate for open radical nephrectomy were included consecutively from 2017 to 2019 at the Urology department of Imam Reza hospital, Mashhad, Iran. Inclusion criteria were patients with T1-T3 renal tumors with no involvement of lymph nodes based on clinical evaluations and computed tomography (CT) images (cN0, cM0). We excluded patients with positive lymph nodes metastasis or with a history of chemotherapy or radiotherapy. In this study, the validity of sentinel lymph node biopsy procedure as our index test was compared with lymphadenectomy as the standard method for staging and detecting the regional lymph nodes metastasis. The study was approved by the local ethics committee of Mashhad University of Medical Sciences under the approval number of 940295. Written informed consent was obtained from all the included patients.

Radiotracer injection

Under general anesthesia, after exposing the tumor, 37 Mbq (1 mCi) of technetium-99m-labelled phytate in 1 mL of saline was injected at two peritumoral sites (0.5 mL each). Figure 1 indicates the injection of the radiotracer in a patient with RCC.

Fig 1. Intraoperative injection of the radiotracer.

Sentinel node biopsy

After the surgical removal of the kidney, sentinel node mapping was conducted using a hand-held gamma probe (SURGEOGUIDE II, Parto Negar Persia Co.). The mean time between the injection of the tracer and performing intraoperative sentinel lymph node mapping was one hour. Lymph nodes with ex vivo count five times more than the background (thigh) and in vivo count ten times more than the background were

dissected as the sentinel lymph node; thirty seconds cumulative count was measured for ex vivo and in vivo counting. Ex vivo counting of the dissected lymph nodes was done using the probe pointed to the ceiling while the lymph nodes were on the tip of the gamma probe. After harvesting of the sentinel lymph nodes accessible through the surgical approach, the area was searched again to confirm the complete sentinel lymph node removal. To evaluate the false-negative rate, lymph node dissection was performed as the standard procedure; lymph nodes removed along the hilar, paracaval and interaorto-caval in patients with right side tumor, and hilar, paraaortal, and interaorto-caval in patients with left side tumor.

Histopathological investigation

The tumor specimen, sentinel lymph nodes, and excised other lymph nodes were carefully examined by the pathologist to detect any metastatic involvement in dissected lymph nodes. The sentinel nodes were step sectioned and evaluated by H&E staining. The histopathological status of the sentinel node was compared with that of all other excised nodes.

Detection rate and false-negative rate

Detection rate (number of patients with at least one hot sentinel node to all patients) and false-negative rate (number of patients with an involved non-sentinel node without sentinel node involvement to all patients with involved lymph nodes in whom at least one sentinel node was detected) were used as the indices of diagnostic performance [15-17].

RESULTS

Twenty-one patients were included in the study. Patients' characteristics are presented in Table 1. Nine patients were female and 12 were male; mean age, 59 years; range, 32-77 years. Fifteen of the patients had a right kidney tumor, and six had left kidney tumors. The median of the primary tumor diameter was 8 (range 1-18 cm). The pT stage of kidney tumor was pT1 in six, pT2 in four, and pT3 in twelve of the patients.

Totally 32 sentinel nodes were excised from 13 patients (median: 2 (min-max:1-5). At least one sentinel lymph node was detected in 13/21 of the patients using a hand-held gamma probe, and the detection rate was 61%. Eight patients had sentinel lymph node detection failure and five of them revealed lymph node metastasis based on the pathology report. Only one of the thirteen patients with successful detected sentinel lymph node revealed lymph node metastasis in both regional lymph nodes and harvested sentinel lymph node from the right renal hilum. There was no patient with positive pathological involvement of the regional lymph nodes despite the negative involvement of the sentinel lymph node; so, the false-negative rate was 0%.

The locations of the detected sentinel lymph nodes were in the right renal hill (6 patients), left renal hill (1 patient), para-aortic (5 patients), and para-caval (1 patient) (Figure 2).

Table 1: Characteristics of the included patients.

Patients		Successful sentinel node detection	Sentinel node detection failure
Gender	Male	8	4
	Female	5	4
Age	Mean	57.5 (32-77)	61.0 (36-76)
	Median	59	66.5
pTstage	T1	5	1
	T2	1	2
	T3	7	5
Size of the tumor (cm) (median)		8	9
Tumor location	Right	9	6
	Left	4	2

Table 2: Data of the similar previous studies compared with the current study.

Study	Year	Country	Patients	Injection material	Injection site	Sentinel lymph node detection rate	Pathologically involved patients	False negative rate
Sherif et al. [18]	2012	Sweden	11	4 injections of 60 – 80 MBq ^{99m}Tc-labelled albumin colloid and 1-2 mL of patent blue	Peritumoral	SPECT/CT: 3/11 Intraoperative: 9/11 Blue dye: 1/8	3	0/3
Kuusk et al. [19]	2018	Netherlands	73	2–3 depots of 225 MBq ^{99m}Tc-nanocolloid	Intratumoral	SPECT/CT: 46/73 Inraoperative: 45/73	2	0/1
Current study	2021	Iran	21	2 injections of 60 – 80 MBq ^{99m}Tc-labelled albumin colloid	Peritumoral	Intraoperative: 13/21	6	0/1

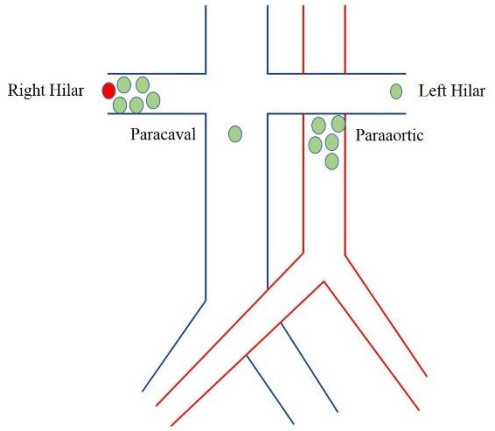

Fig 2. Location of the detected sentinel lymph nodes in each patient. (The red color sentinel node is the metastatic sentinel node and the green color sentinel nodes are without metastasis).

DISCUSSION

Sentinel lymph node biopsy plays a significant role in studying the lymphatic system drainage and lymphatic staging of the solid tumors through a less aggressive approach than lymph node dissection. The sentinel lymph node mapping has been approved for many cancers, including breast cancer, melanoma, head and neck, gynecological and gastrointestinal malignancies; however, it is under investigation in urological cancers such as prostate, bladder, and testicular tumors [4, 10, 15, 17].

Based on our results, lymphatic mapping with an intraoperative gamma probe was successful in 13/21 (61%) of the patients by detecting one or more sentinel lymph nodes in each patient. The feasibility of the sentinel lymph node biopsy in renal carcinoma has also been evaluated by two previous groups. In a study by Sherif et al. [18], the intraoperative gamma probe technique on the day of surgery was successful in detecting the sentinel lymph node in 9 out of 11 patients. However, lymphoscintigraphy (SPECT/CT) revealed the sentinel lymph node in only 3 of the 11 patients (27%), injected through laparoscopy in the mentioned study. Kuusk et al. [19] showed a similar detection rate with our result; they detected sentinel lymph nodes in 45/73 (61%) performing lymphoscintigraphy (SPECT/CT) and the following intraoperative gamma probe technique on the day of surgery.

Due to unpredictable lymphatic drainage from RCC, wide heterogeneity and variability of lymphatic vessels, and sparse evidence on anatomic templates of lymph node dissection [20-22], the sentinel lymph node mapping technique might has the potential to enhance the current knowledge in this regard. However, for validating sentinel lymph node procedure in these patients, several factors including dosage of the radiotracer, the preferred injecting techniques, and imaging protocol are needed to be optimized and standardized [23-26]. There were considerable differences between previous studies on sentinel lymph node biopsy of the RCC patient, regarding the injected radiotracer dose, injection site, and the method of mapping (Table 2).

Sentinel lymph node detection failure was 8/21 (37%) in our study, which was similar to the study of Kuusk et al. (27/73) and higher than the study of Sherif et al. (2/11). Three of the eight patients with no sentinel lymph node detected, did not have any tumoral involvement of the lymph nodes. In five of these eight patients with no detected sentinel lymph node, the pathological evaluation of the harvested lymph nodes, reported the presence of tumoral cells. The metastatic involvement of the lymph nodes can be a significant

reason for the non-visualization of the sentinel lymph node in these patients. This is most likely due to various factors including nodal tumor load, and occlusion of lymphatic vessels by tumor cells. Besides, high vascularity of the kidney increases the risk of radiotracer washout in kidney tumors, which can contribute to sentinel node detection failure in our study.

Only one of our evaluated patients showed pathological involvement of the detected sentinel lymph node, who also had positive involvement of other dissected lymph nodes in the pathology report (no false negative case). So, although 6 of the 21 (28%) included patients showed pathologically involved lymph nodes, sentinel lymph node detection failure was observed in five of them.

In our study, the radiotracer was injected in healthy tissue around the tumor (peritumoral), which is accepted in other cancers, including breast cancer, melanoma, thyroid, etc. [27, 28]. Based on some previous reports, the peritumoral injection of the radiotracers resulted in a higher sentinel node detection rate compared with intratumoral injection. In the study of Sherif et al. [18], the radiotracer was also injected in a peritumoral fashion with sentinel node detection in nine out of eleven included patients, using a hand-held gamma probe. In the study of Kuusk et al. [19], the radiotracer was injected intratumorally and revealed a lower detection rate than the Sherif et al. study. However, Due to the high vascularity of the kidney compared to other organs, in both injecting methods, there might be the possibility of radiotracer washout.

According to the previous studies, preoperative SPECT/CT images do not considerably increase the sentinel node detection rate compared with the method of intraoperative sentinel node mapping in RCC patients. The intense activity of the injection site might negatively affect the separation and detection of the close sentinel lymph nodes on the images and decrease the detection rate. As the study of Sherif et al. showed, the sentinel lymph node detection rate of preoperative lymphoscintigraphy was 3/11 patients (with 73% detection failure), which was lower than the sentinel lymph node detection rate of 9/11 through the intraoperative sentinel lymph node mapping method (18% detection failure) [18]. The study of Kussk et al. revealed a similar detection rate between preoperative SPEC/CT (63%) and intraoperative sentinel node mapping (61%) [19]. So, despite the safety and feasibility of the SPECT/CT for sentinel lymph node mapping of the patients with renal cancer, performing this method has not increased the sensitivity of the sentinel node mapping procedure and has shown a high non-visualization rate based on the previous studies [19]. In our study, the injection of radiotracer was done intraoperatively and SPECT/CT lymphoscintigraphy was not possible.

The main limitation of our study was the small number of the patients with pathological involvement of the lymph node. By increasing the patients sample size in future studies, this limitation will be resolved.

CONCLUSION

Although sentinel lymph node biopsy was feasible in patients with RCC, sentinel node detection failure was high in our study. More prospective studies with a larger sample size are needed for standardization of the radiotracer injecting aspects and mapping method to increase the detection rate and to evaluate the false negative rate more accurately.

Acknowledgements

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

REFERENCES

1. Capitanio U, Becker F, Blute ML, Mulders P, Patard JJ, Russo P, Studer UE, Van Poppel H. Lymph node dissection in renal cell carcinoma. Eur Urol. 2011;60(6):1212-20.
2. Stabile A, Muttin F, Zamboni S, Moschini M, Gandaglia G, Fossati N, Dell'Oglio P, Capitanio U, Cucchiara V, Mazzone E, Bravi CA, Mirone V, Montorsi F, Briganti A. Therapeutic approaches for lymph node involvement in prostate, bladder and kidney cancer. Expert Rev Anticancer Ther. 2019 Sep;19(9):739-755.
3. Cabanas RM. An approach for the treatment of penile carcinoma. Cancer 1977;39(2):456-66.
4. 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;187(1):25-31.
5. 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;38(2):95-109.
6. Ansari M, Rad MA, Hassanzadeh M, Gholami H, Yousefi Z, Dabbagh VR, Sadeghi R. Sentinel node biopsy in endometrial cancer: systematic review and meta-analysis of the literature. Eur J Gynaecol Oncol. 2013;34(5):387-401.
7. Farazestanian M, Yousefi Z, Zarifmahmoudi L, Mofrad MH, Kadkhodayan S, Sadeghi R. Concordance between intracervical and fundal injections for sentinel node mapping in patients with endometrial cancer?: a study using intracervical radiotracer and fundal blue dye injections. Clin Nucl Med. 2019;44(3):e123-e27.
8. Hassanzadeh M, Farahabadi EH, Yousefi Z, Kadkhodayan S, Zarifmahmoudi 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;9(1):55.

9. Sadeghi R, Asadi M, Treglia G, Zakavi SR, Fattahi A, Krag DN. Axillary concordance between superficial and deep sentinel node mapping material injections in breast cancer patients: systematic review and meta-analysis of the literature. Breast Cancer Res Treat. 2014;144(2):213-22.

10. Sadeghi R, Tabasi K, Bazaz S, Kakhki V, Massoom A, Gholami H, Zakavi S. Sentinel node mapping in the prostate cancer: meta-analysis. Nuklearmedizin. 2011;50(3):107-15.

11. Bersanelli M, Buti S, Santoni M, Ziglioli F, Maestroni U. Pathological nodal staging score for renal cell carcinoma: how to build reliable therapeutic choices basing on assumptions. Ann Transl Med. 2019;7(Suppl 1):S54.

12. Bhindi B, Wallis CJ, Boorjian SA, Thompson RH, Farrell A, Kim SP, Karam JA, Capitanio U, Golijanin D, Leibovich BC. The role of lymph node dissection in the management of renal cell carcinoma: a systematic review and meta-analysis. BJU international. 2018;121(5):684-98.

13. Kim BS, Yoo ES, Kim TH, Kwon TG. Chylous ascites as a complication of laparoscopic nephrectomy. J Urol. 2010;184(2):570-4.

14. Capitanio U, Leibovich BC. The rationale and the role of lymph node dissection in renal cell carcinoma. World J Urol. 2017 Apr;35(4):497-506.

15. Zarifmahmoudi L, Sadeghi R. Re: radio-guided lymph node mapping in bladder cancer Using SPECT/CT and intraoperative γ-probe methods. Clin Nucl Med. 2017 Apr;42(4):327.

16. 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;19(10):918-22.

17. Sadeghi R. Sentinel node mapping diagnostic studies warrant a unique reporting criteria: comment on Xiong et al. systematic review. Eur J Surg Oncol. 2014;40(8):1025-6.

18. Sherif AM, Eriksson E, Thorn 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(8):1134-9.

19. Kuusk T, Donswijk ML, Valdes Olmos RA, De Bruijn RE, Brouwer OR, Hendricksen K, Horenblas S, Jozwiak K, Prevoo W, Van Der Poel HG, Van Rhijn BWG, Wit EM, Bex A. An analysis of SPECT/CT non-visualization of sentinel lymph nodes in renal tumors. EJNMMI Res. 2018;8(1):105.

20. Hulten L, Rosencrantz M, Seeman T, Wahlqvist L, Ahren C. Occurrence and localization of lymph node metastases in renal carcinoma. A lymphographic and histopathological investigation in connection with nephrectomy. Scand J Urol Nephrol. 1969;3(2):129-33.

21. Saitoh H, Nakayama M, Nakamura K, Satoh T. Distant metastasis of renal adenocarcinoma in nephrectomized cases. J Urol. 1982;127(6):1092-5.

22. Mahon TG, Libshitz HI. Mediastinal metastases of infradiaphragmatic malignancies. Eur J Radiol. 1992;15(2):130-4.

23. Karmali RJ, Suami H, Wood CG, Karam JA. Lymphatic drainage in renal cell carcinoma: back to the basics. BJU Int. 2014;114(6):806-17.

24. Moschini M, Dell'Oglio P, Larcher A, Capitanio U. Lymph node dissection for renal cell carcinoma: what are we missing? Curr Opin Urol. 2016;26(5):424-31.

25. Ljungberg B, Albiges L, Abu-Ghanem Y, Bensalah K, Dabestani S, Fernández-Pello S, Giles RH, Hofmann F, Hora M, Kuczyk MA, Kuusk T, Lam TB, Marconi L, Merseburger AS, Powles T, Staehler M, Tahbaz R, Volpe A, Bex A. European association of urology guidelines on renal cell carcinoma: The 2019 update. ur Urol. 2019 May;75(5):799-810.

26. Motzer RJ, Jonasch E, Michaelson MD, Nandagopal L, Gore JL, George S, Alva A, Haas N, Harrison MR, Plimack ER. NCCN Guidelines Insights: Kidney Cancer, Version 2.2020. J Natl Compr Canc Netw. 2019 .Nov 1;17(11):1278-1285.

27. Assadi M, Yarani M, Zakavi SR, Jangjoo A, Memar B, Treglia G, Aliakbarian M, Mehrabibahar M, Sadeghi R. Sentinel node mapping in papillary thyroid carcinoma using combined radiotracer and blue dye methods. Endokrynol Pol. 2014;65(4):281-6.

28. Motamedolshariati M, Rezaei E, Beiraghi-Toosi A, Jahani A, Tayyebi Meibodi N, Fattahi A. Sentinel node mapping in Marjolin's ulcers: is it feasible. Wounds. 2015;27(3):54-62.