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Original

Sentinel lymph node biopsy in upper tract urothelial cancers: an experience with intraoperative radiotracer injection

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ABSTRACT

Background: The feasibility of the sentinel node mapping in upper tract urothelial cancers (UTUC) was evaluated, using a radiotracer as the mapping material.

Material and methods: To identify the sentinel lymph nodes, 37 MBq of [^{99m}Tc] phytate was injected in five patients with the renal pelvis or ureter cancer, who were candidates for ureterectomy and lymphadenectomy. The radiotracer was injected in a peritumoral fashion following the surgical exposure of the tumour. The sentinel lymph nodes were detected using a hand-held gamma probe.

Results: By intraoperatively injecting the radiotracer immediately after surgical exposure of the tumour, at least one sentinel lymph node could be detected in each patient, and the detection rate was 100%. The location of sentinel nodes was in the paracaval, renal hill, retro-aortic, para-aortic, common iliac, and external iliac areas, which was dependent on the tumour location. No false-negative case was identified.

Conclusions: Sentinel node mapping is feasible in UTUC. Injection technique (intra-vesical approach vs peri-tumoral injection after exposure of the tumour) and location of the tumour (proximal vs distal) may affect the technique's feasibility.

KEY words: lymphoscintigraphy; nuclear medicine; ureter; renal pelvis; sentinel lymph node biopsy; lymphadenectomy

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Introduction

Urothelial carcinomas can be originated from lower (bladder and urethra) or upper (pyelocaliceal cavities and ureter) parts of the urinary tract [1]. Bladder carcinomas (lower tract urothelial carcinomas) account for 90–95% of the urinary tract malignancies; however, the upper urinary tract (UUT) transitional cell carcinoma (TCC) is an uncommon type of malignancies and accounts for 5–10% of urinary tract cancers [2, 3]. Tumours of the ureter are particularly rare compared to bladder cancer or renal pelvis tumours, despite sharing common histopathology and similar risk factors [4].

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The most common treatment option for high-grade tumours originate in the upper ureter and renal pelvis, is nephroureterectomy followed by regional lymph node dissection (LND); however, due to the low incidence of the upper tract urinary carcinoma (UTUC), the indication and extent of LND is not standardized [5]. The risk of lymph node involvement increases with the T stage of the disease, and up to 60% of UTUCs demonstrate local invasion at diagnosis [6]. LND is recommended to be performed based on the laterality and tumour location following nephroureterectomy; however, due to variable lymphatic drainage and lack of consensus on anatomical boundaries, the potential benefit of routine LND on survival or disease recurrence remains controversial [7, 8].

Sentinel lymph node mapping procedure is used for detecting the first lymph node in the path of lymphatic drainage of cancers. This technique reveals the pathological status of the regional lymph nodes for the better staging of the disease, determining the treatment strategy, and preventing the unnecessary LND. Sentinel lymph node biopsy is routinely performed for breast cancer,

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malignant melanoma, gynaecological, and penile tumours; however, for other urologic genitourinary carcinomas, it is still under investigation [9–14].

The present study evaluated the feasibility of sentinel node mapping in UTUC using a radiotracer as the mapping material.

Material and methods

This study was approved by the ethics committee of Mashhad University of Medical Sciences under the number 940295. Between 2016 and 2019, all the admitted UTUC patients at the urology department of Imam Reza Hospital, Mashhad, Iran, were included. All the patients gave their informed consent before inclusion in the study. Patients with negative lymph node involvement before the surgery, based on clinical and radiological evaluations (cN0, cM0) were included. The exclusion criteria were positive lymph nodes metastasis and a history of chemotherapy or radiotherapy.

Radiotracer injection

Following anaesthesia, 37 MBq of [^{99m}Tc]phytate in two divided doses (0.5 mL each) were used as the radiotracer. In the first four patients with TCC of the distal part of the ureter, the radiotracer was injected sub-mucosally in the peritumoral area of the tumour through ureteroscopy. These patients were excluded from the study due to sentinel lymph node detection failure. The injection technique was changed in five other patients: the radiotracer was injected into two peritumoral sites following the tumour's exposure (Tab. 1, Fig. 1).

Sentinel node biopsy

The mean time between the tracer injection and performing intraoperative sentinel lymph node mapping was one hour. Following the excision of the ureter and kidney and before starting lymphadenectomy, a hand-held gamma probe (SURGIGUIDE, Partonegar Persia) was used to measure the radioactivity and perform sentinel node biopsy. The sentinel lymph nodes were defined as any lymph node with an in-vivo count of at least ten times higher than the background (thigh). These nodes were dissected and counted again ex-vivo. The dissected lymph nodes were put on the tip of the gamma probe while the probe was pointed to the ceiling. All the lymph nodes with ex-vivo count five times higher than the background (thigh) were eventually determined as the sentinel lymph node.

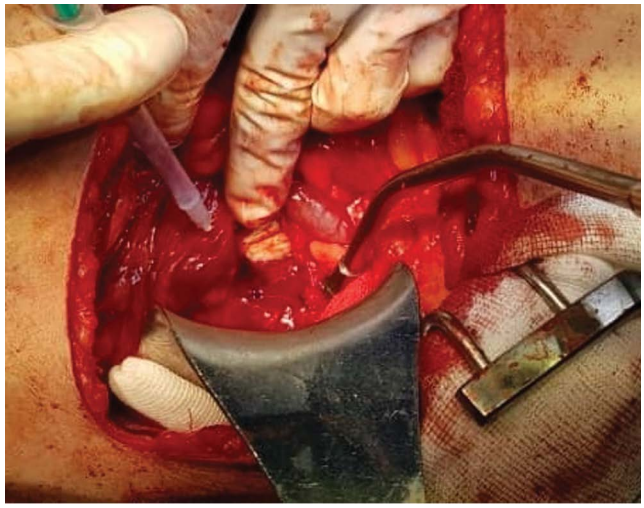

Figure 1. Injection of the radiotracer in a patient with mid-urethral tumour, after the surgergical exposure of the tumour

After harvesting the detected sentinel lymph nodes, the surgical area was searched again to confirm the complete sentinel lymph node removal.

Regional lymphadenectomy was performed based on the surgeon's decision to assess the false-negative rate. For the left-sided renal pelvis, upper ureteral, and mid-urethral tumours, the lymphadenectomy dissection area covered para-aortic, pre-aortic, and inter-aortocaval nodes from the renal hilum to the aortic bifurcation. For the right-sided renal pelvis and upper ureteral tumours, mid-urethral tumours lymph nodes of the paracaval, precaval, and interaortocaval areas from the renal hilum to the aortic bifurcation are considered for lymphadenectomy. Common iliac, external iliac, obturator, and hypogastric lymph nodes of each side of the pelvic are also dissected for mid to distal ureteral tumours.

Table 1. Detailed data of the included patients

Patients	Gender	age	Tumor location	kidney	Tumor stage	Tumor larger diameter (cm)	Detection of the SN	SN location	Number of SN	Involvement of SN	Involvement of lymph nodes
1	M	53	Middle	right	T3	2.5	Yes	Paracaval	3	Yes 1/3	Yes (paracaval)
2	M	74	Proximal	Left	T1	2.7	Yes	Renal hill	2	No	No
3	M	40	Renal pelvis (proximal)	Right	T3	4 × 2	Yes	Renal hill	2	No	No
4	M	80	Distal	Right	T2	4.5	Yes	Common iliac external iliac	2	No	No
5	F	48	Renal pelvis (proximal)	left	T2	4	Yes	Retroaort and Paraaort	2	No	No

SN — sentinel node

Histopathological investigation

The pathologists examined the excised lymph nodes and specimen; all dissected tissues were formalin-fixed, paraffin-embedded, and serially sectioned for haematoxylin-eosin staining. The histopathological status of the sentinel nodes was compared with the other dissected lymph nodes.

Evaluated indices (detection rate and false-negative rate)

The primary endpoints of the study were sentinel node detection rate and false-negative rate (FNR).

The detection rate was measured as the ratio of all cases with at least one detected sentinel node to all included patients. The false-negative rate was measured as the ratio of patients with involved non-sentinel lymph nodes despite pathologically free sentinel lymph nodes to all patients with involved nodes and at least one harvested sentinel node [15, 16].

Results

Five patients with renal pelvis or ureter cancer were included; four patients were male, and one was female with a mean age of 59.

The tumour was localized in proximal ureter in two patients, distal ureter in one patient, and middle ureter in one patient.

Demographic data and information regarding the sentinel lymph node detection are summarized in Table 1.

Detection rate

In all patients with the peritumorally injection of the radiotracer following the surgical exposure of the tumour, at least one sentinel node was detected. The detection rate was 100% in these five patients, and eleven (median = 2) sentinel lymph nodes were dissected in total (Fig. 1).

All the patients with no detected sentinel node were injected through the ureteroscopy at two sites around the visible tumour; so, the detection rate was zero in UTUC patients with ureteroscopic injections; these patients were excluded from the study.

The detected sentinel nodes were in the paracaval lymph nodes (patient 1), renal hilum lymph nodes (patients 2 and 3), retro aortic and para-aortic lymph nodes (patient 5), and common iliac and external iliac lymph nodes (patient 4).

False-negative rate

One patient (number 1) had pathological involvement of the dissected sentinel lymph node. The detected sentinel nodes were in paracaval area (three sentinel nodes), and one showed tumoral involvement. Based on the pathology report, the non-sentinel paracaval lymph nodes dissected in this patient were also pathologically involved.

No lymph node involvement was noted in the remaining four patients (no false-negative result).

Discussion

Upper urinary tract TCCs are among the rare types of genitourinary tumours which develop in the renal pelvis and ureter and might be associated with bladder cancer. To the authors' knowledge, they evaluated the feasibility of the sentinel node mapping approach for the first time in patients with UTUC including, patients with TCCs in the proximal, middle, and distal parts of the ureter and also in the renal pelvis. They used Tc-99m phytate as the mapping material, and no blue dye was used due to the reported adverse reaction to the blue dye injection [17, 18].

The detection rate in this study was highly dependent on the injection method of the radiotracer. In patients with the ureteroscopic injection of the tracer, no sentinel node could be identified intra-operatively. So, these patients were excluded from the study and changed the injection technique. In the remaining patients (five patients) with radiotracer injection following the tumour exposure during the surgery, at least one sentinel node could be identified. These results are most likely due to the technical difficulty of injection through a ureteroscope. The movement of the radiotracer in the lymphatic system is reasonably fast, which ensures a successful mapping using an intra-operative injection of the tracer [19–21].

Although LND is performed for better staging of the tumour, due to the low prevalence of UTUC, the curative role of LND continues to be debated, and LND is not currently performed in all patients worldwide. In patients with the T1 stage of the disease, there might be a low probability of the LN metastases, and LND does not seem to improve the staging. All the current evidence on UTUC is based on retrospective studies with a limited study population. To precisely determine the indication of LND and its optimal template, which varies according to the location of the disease, more extensive studies should be performed [22–27]. Although the LND template has been studied previously, there is no standardized template for LND, and it is dependent on the site of the affected ureter [1, 28].

Based on the present results, sentinel lymph nodes as the first lymph nodes which receive the metastatic cells were located in the renal hilum, retro-aortic, and para-aortic lymph nodes of the patients with TCCs in the proximal part of the left ureter or the left renal pelvis. However, in two patients with TCCs in the middle part of the right ureter and the right renal pelvis, the detected sentinel lymph nodes were in paracaval and right renal hilum lymph nodes. The sentinel lymph nodes in one of the study patients with TCC in the distal part of the right ureter was in the common iliac and external iliac lymph nodes. The present results were in accordance with the previous studies in this regard. Kondo et al. [22] proposed that the paracaval, retrocaval, and interaortocaval nodes have a higher risk of metastases in patients with the right renal pelvis and upper two-thirds of the ureter tumours and should be included in the LND template. On the other hand, the renal hilum and para-aortic nodes in patients with left renal pelvis tumours should be considered in the LND template.

We included only patients with no lymph node involvement based on preoperative imaging; however, these modalities have shown limited accuracy for preoperative LN staging or identifying patients with LN invasion [29, 30]. LND in patients with UTUC is highly surgeon-dependent due to inaccurate prediction tools, and sentinel lymph node mapping might be of value to find the metastatic status of the regional lymph nodes. This study showed that sentinel node could be detected in all the UTUC patients with the intraoperative injection of the radiotracer mapping, and sentinel lymph node mapping might be a feasible method in patients with tumours in different parts of the ureter or renal pelvis. However, more extensive studies (preferably multicentral) are needed before any definitive conclusion.

The major limitation of the present study was the low sample size due to the low incidence of UTUC. However, to the authors' knowledge, this study is the first study on intraoperative sentinel lymph node mapping in UTUC tumours, which obtained promising results.

Conclusions

Sentinel node mapping is feasible in UTUC. Injection technique (intra-vesical approach vs peri-tumoral injection after exposure of the tumour) and location of the tumour (proximal vs distal) might affect the technique's feasibility.

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