Sentinel nodes in complex areas: innovating radioguided surgery
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Chapter 14

Lymphatic drainage from the treated versus untreated prostate: feasibility of sentinel node biopsy in recurrent cancer

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ABSTRACT

Purpose: To establish the feasibility of sentinel node biopsy in patients with recurrent prostate cancer after initial local treatment, and to compare lymphatic drainage patterns of the treated versus untreated prostate.

Methods: In ten patients with a proven local recurrence after initial local treatment (four external beam radiation, four brachytherapy, two high-intensity-focused-ultrasound), the radiotracer (99mTechnetium-nanocolloid, GE Healthcare) was injected into the prostate. Planar images after fifteen minutes and two hours were followed by SPECT/CT (SymbiaT, Siemens) to visualise lymphatic drainage. Laparoscopic sentinel lymphadenectomy was assisted by a gamma probe (Europrobe, Euro Medical Instruments) and a portable gamma camera (Sentinella, Oncovision). Sentinel node identification and lymphatic drainage patterns were compared to a consecutive series of seventy untreated prostate carcinoma patients from our institute.

Results: Lymphatic drainage was visualised in all treated patients, with a median of 3.5 sentinel nodes per patient. Most sentinel nodes were localized in the pelvic area, although the percentage of patients with a sentinel node outside the pelvic para-iliac region (para-aortic, pre-sacral, inguinal or near the ventral abdominal wall) was high compared to the untreated patients (80% vs. 34%, p=0.01). In patients with recurrent prostate cancer, ninety-five percent of the sentinel nodes could be harvested and half of the patients had at least one positive sentinel node on pathological examination.

Conclusions: Lymphatic mapping of the treated prostate appears feasible, although sentinel nodes are more frequently found in an aberrant location. Larger trials are needed to assess sensitivity and therapeutic value of lymphatic mapping in recurrent prostate cancer.
INTRODUCTION

Sentinel lymphadenectomy for prostate cancer is an accurate staging procedure and is frequently used at our institute.\textsuperscript{1-6} Sentinel node mapping has several advantages over pelvic lymphadenectomy. It is a less invasive procedure, causes less morbidity and sentinel nodes outside the area of pelvic lymphadenectomy region can also be sampled.\textsuperscript{1,6,7}

Previously administered treatment might influence lymphatic flow. In breast cancer, previous surgery as well as radiotherapy have been reported to lead to higher rates of non-visualisation of sentinel nodes and higher percentages of extra-axillary drainage.\textsuperscript{8,9} Estourgie et al. have demonstrated that lymphatic mapping before and after wide local excision of a breast tumour does not show reproducible results.\textsuperscript{10} Authors of several recent publications suggest that lymphatic mapping in previously treated patients is feasibly though.\textsuperscript{8,9,11-15} Furthermore, a recent study from our institute has demonstrated the feasibility of repeat sentinel node biopsy in patients with recurrent penile carcinoma.\textsuperscript{16}

No literature is available on sentinel lymphadenectomy after local treatment of prostate cancer, but administration of radiotherapy might influence lymphatic drainage, as it does in the breast. If prostate cancer progresses or recurs after initial treatment, a sentinel lymphadenectomy can be useful to exclude the presence of lymph node metastases before salvage treatment is considered. The goal of the current study was to establish the feasibility of sentinel node biopsy in previously treated patients with recurrent prostate cancer, and we evaluated lymphatic drainage patterns of the treated prostate in comparison to untreated patients.

PATIENTS AND METHODS

Patients

We included ten patients who were referred to our institute with a local recurrence of prostate cancer after initial treatment. Mean time between first treatment and recurrence was sixty months (range 10-109 months). All patients had biopsy proven recurrent carcinoma, except for one patient in whom the FDG-PET-scan had shown the recurrence in the prostate (patient 4, table 1). Patients were considered candidates for salvage treatment. Initial local treatment had consisted of local external beam radiation in four patients, brachytherapy in four patients and high-intensity-focused-ultrasound in two patients. In all patients, treatment had been confined to the prostate; the pelvic area had not been irradiated. The patients that
Table 1 | Patient characteristics and lymphatic drainage of treated patients. Patients are mentioned in order of presentation and treatment of the recurrence.

<table>
<thead>
<tr>
<th>Initial tumour characteristics</th>
<th>Treatment regime</th>
<th>Preoperative lympho-scintigraphy</th>
<th>Preoperative SPECT/CT</th>
<th>Intra-operative findings</th>
<th>Pathology</th>
<th>Regime</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNM: cT1cN0xM0</td>
<td>Gleasonscore: 8</td>
<td>PSA: 7.4 ng/ml</td>
<td>External beam radiotherapy and hormonal treatment</td>
<td>1 SN pelvis R</td>
<td>4 SN obt fossa R</td>
<td>All sentinel nodes harvested except 1 presacral node (promontorium)</td>
</tr>
<tr>
<td>TNM: cT3NxMx</td>
<td>Gleasonscore: 7</td>
<td>PSA: 5.1 ng/ml</td>
<td>External beam radiotherapy and hormonal treatment</td>
<td>1 SN pelvis R</td>
<td>1 SN bifurcation art.</td>
<td>Sentinel node harvested</td>
</tr>
<tr>
<td>TNM: cT1cN0xM0</td>
<td>Gleasonscore: 6</td>
<td>PSA: 8.2 ng/ml</td>
<td>Brachytherapy</td>
<td>1 SN pelvis L</td>
<td>1 SN obt fossa L</td>
<td>All sentinel nodes harvested</td>
</tr>
<tr>
<td>TNM: cT2cN0xM0</td>
<td>Gleasonscore: 6</td>
<td>PSA: 2.2 ng/ml</td>
<td>High-intensity-focused-ultrasound</td>
<td>2 SN pelvis R</td>
<td>1 SN obt fossa L</td>
<td>All sentinel nodes harvested</td>
</tr>
<tr>
<td>TNM: cT2NxMx</td>
<td>Gleasonscore: 7</td>
<td>PSA: 5.1 ng/ml</td>
<td>Brachytherapy</td>
<td>1 SN pelvis L</td>
<td>2 SN obt fossa L</td>
<td>All sentinel nodes harvested</td>
</tr>
<tr>
<td>TNM: cT2aNxMx</td>
<td>Gleasonscore: 7</td>
<td>PSA: 2.3 ng/ml</td>
<td>External beam radiotherapy and hormonal treatment</td>
<td>1 SN pelvis L</td>
<td>1 SN obt fossa L</td>
<td>All sentinel nodes harvested</td>
</tr>
<tr>
<td>TNM: cT1bNxMx</td>
<td>Gleasonscore: 3</td>
<td>PSA: 8 ng/ml</td>
<td>Trans-urethral prostate resection, external beam radiotherapy and hormonal treatment</td>
<td>1 SN pelvis L</td>
<td>2 SN obt fossa L</td>
<td>All sentinel nodes harvested</td>
</tr>
</tbody>
</table>

Hormonal treatment will be started on indication (PSA rise or bone metastases)
<table>
<thead>
<tr>
<th>Initial tumour characteristics</th>
<th>Treatment regime</th>
<th>Preoperative lympho-sцинтigraphy</th>
<th>Preoperative SPECT/CT findings</th>
<th>Intra-operative findings</th>
<th>Pathology</th>
<th>Regime</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNM: cT2cNxMx</td>
<td>High-intensity-focused-ultrasound</td>
<td>2 SN pelvis L, 1 SN pelvis R</td>
<td>1 SN obt fossa L, 1 SN obt fossa R, 1 SN paravesical L</td>
<td>All sentinel nodes harvested except paravesical node</td>
<td>Negative</td>
<td>Salvage brachytherapy</td>
</tr>
<tr>
<td>Gleason score: 8</td>
<td></td>
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<tr>
<td>PSA: 30 ng/ml</td>
<td></td>
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<tr>
<td>TNM: cT2cNxMx</td>
<td>Brachytherapy</td>
<td>1 SN pelvis L, 1 SN inguinal R</td>
<td>1 SN obt fossa L, 1 SN inguinal R</td>
<td>Both sentinel nodes Positive (1/2) harvested</td>
<td></td>
<td>No salvage prostatectomy</td>
</tr>
<tr>
<td>Gleason score: 6</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>PSA: 10 ng/ml</td>
<td></td>
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</tr>
<tr>
<td>TNM: cT NxMx</td>
<td>Brachytherapy</td>
<td>1 SN pelvis L, 2-3 SN pelvis R</td>
<td>2 SN obt fossa L, 1 SN paravesical L, 2-3 SN obt fossa R</td>
<td>All sentinel nodes harvested</td>
<td>Negative</td>
<td>Salvage prostatectomy</td>
</tr>
<tr>
<td>Gleason score: 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA: 11.6 ng/ml</td>
<td></td>
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</table>

SN= sentinel node, obt fossa=obturator fossa, L=left, R=right, mid-abd=mid-abdominal
had received external beam radiotherapy had also been given hormonal treatment at initial diagnosis, which had not been the case in the other six patients (table 1).

Sentinel lymph node mapping was performed to determine the additional treatment regime. Patients were included after informed consent between November 2006 and December 2009.

Untreated patients
Results of lymphatic mapping were compared to a consecutive group of seventy patients with untreated prostate cancer from the same period. These untreated patients had primary prostate cancer of the intermediate prognostic group (clinical stage >T2b, or PSA level >10.0 ng/ml, or Gleason sum score above six) and elected to be treated with radiotherapy. Sentinel node biopsy was performed to determine additional treatment regimen. The procedure for sentinel node detection (tracer injection, imaging and operation) was the similar to the procedure in treated patients and is described below.

Sentinel node negative patients received external beam radiation therapy to the prostate (78 Gy) and six months of hormonal treatment. For sentinel node positive patients, our policy was to perform external beam radiation therapy to the prostate (70Gy) and pelvic area (50Gy) and give three years of hormonal therapy. Hormonal therapy was started around the time of sentinel node biopsy.

Image acquisition and sentinel node localization
The radiotracer (99mTechnetium-nanocolloid; GE healthcare, Eindhoven, The Netherlands) was injected in one deposit of 0.1ml in each prostate quadrant, regardless of the location of tumour recurrence. Administration was performed transrectally and guided by transrectal ultrasonography and injection of each tracer deposit was followed by flushing with approximately 0.7ml of saline. Rest radioactivity in the injection device was subtracted from the injected dose to calculate net injected doses. Mean injected dose was 204 Mbq (range 123–235). After injection, preoperative lymphoscintigraphy was performed after fifteen minutes and two hours, directly followed by SPECT/CT two hours after injection. All images were made using a hybrid dual head gamma camera (SymbiaT, Siemens, Erlangen, Germany).

The first nodes in each nodal basin appearing on early planar lymphoscintigraphy were considered to be the sentinel nodes. Nodes appearing later in the same basins were considered to be second echelon nodes. If SPECT/CT showed additional hotspots in caudal areas or on
a side with no other/previous drainage, those hotspots were also considered to be sentinel nodes.

Radioguided sentinel lymphadenectomy was performed within six hours after administration of the radiotracer and was assisted by a laparoscopic gamma probe (Europrobe, Euro Medical Instruments, Le Chesnay, France) and a portable gamma camera (Sentinella, Oncovision, Valencia, Spain). All detected hot spots in the area of the previously defined sentinel nodes were removed. Second echelon nodes, as identified preoperatively, were left in place. All removed nodes were examined by experienced pathologists.

Analysis
Patient, tumour and treatment characteristics were recorded. Primary outcome characteristics were: visualisation of lymphatic drainage, number of sentinel nodes identified pre- and intra-operatively, and location of the sentinel nodes. The location of the sentinel nodes was determined in relation to the “pelvic para-iliac region”. This region was considered to be the region along the external iliac artery between the obturator nerve, pelvic wall and crossing of the ureter over the common iliac artery as well as the region along the internal iliac artery just past the superior vesical artery. We choose this region, because it is the region that is routinely cleared if an extended pelvic lymphadenectomy is performed. SPECT/CT was used as gold standard to define number and location of the sentinel nodes.

The untreated control group was used to compare visualisation of lymphatic drainage and location of the sentinel nodes. The Fisher’s Exact Test (SPSS 15.0 for Windows) was used to analyse association between previously administered treatment and lymphatic drainage towards aberrant locations and association between previously administered treatment and presence of positive sentinel nodes. Other patient characteristics (age, number of sentinel nodes visualised and injected dose of radioactivity) were compared between treated and untreated patients with the Wilcoxon Rank-Sum Test (SPSS 15.0 for Windows). Level of significance was p=0.05.

RESULTS
Lymphatic drainage after prostate irradiation
Table 1 shows patient characteristics of the treated patients, as well as the pre- and intra-operative findings. All ten patients showed direct drainage towards at least one pelvic para-iliac sentinel node, while bilateral pelvic para-iliac drainage was visualised in eight patients. In
80% of the patients a sentinel node outside the pelvic para-iliac region was visualised. Para-aortic sentinel nodes were seen in three patients and a pre-sacral sentinel node was found in one patient. Three patients had a sentinel node near the ventral abdominal wall (para-vesical sentinel node) and another patient had an inguinal sentinel node. Figure 1 shows an overview of all visualised sentinel nodes in the group with recurrent prostate cancer. One sentinel node could not be harvested intra-operatively due to its deep location directly ventral of the promontorium and one para-vesical node could not be identified intra-operatively despite of rigorous searching with the gamma probe. All other sentinel nodes (95%) were excised. Half of the patients had a positive sentinel node on pathological examination. All positive sentinel nodes were localized along the external iliac artery (figure 1). When nodal metastases were demonstrated we refrained from a salvage treatment (prostatectomy or cryotherapy of the prostate) (table 1).

![Figure 1](image.png)

**Figure 1** | Lymphatic drainage patterns of the treated prostate. All sentinel nodes, as preoperatively visualised are shown its anatomic context. The four most caudal nodes represent theinguinal and paravesical sentinel nodes respectively. Nodes that appeared to be tumour-positive on pathological examination are highlighted with a yellow mark.

**Comparison of drainage patterns**

Number of sentinel nodes per patient, age and injected dose did not differ significantly between treated and untreated patients (table 2). In the untreated group significantly fewer nodes were found outside the pelvic para-iliac region (34% versus 80%, \( p=0.01 \)). Thirty-four percent of the untreated prostate cancer patients had one or more positive nodes. This number was higher in patients with recurrence (50%), although the difference was not significant.
Table 2 | Comparison of patient characteristics and lymphatic drainage

<table>
<thead>
<tr>
<th></th>
<th>Untreated N=70</th>
<th>After treatment N=10</th>
<th>Difference (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>64 (range 53–78)</td>
<td>67 (range 61–74)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Mean injected dose (M bq)</td>
<td>215 (range 147–286)</td>
<td>204 (range 123–235)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Visualisation of lymphatic drainage</td>
<td>99%</td>
<td>100%</td>
<td>n.s.</td>
</tr>
<tr>
<td>Number of SN visualised (SPECT-CT)</td>
<td>Mean: 3.8 Median: 3</td>
<td>Mean: 4 Median: 3.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>Patients with uncommonly located SN (%)</td>
<td>34%</td>
<td>80%</td>
<td>p=0.01</td>
</tr>
<tr>
<td>(outside pelvic para-iliac area)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Node positive patients (%)</td>
<td>34%</td>
<td>50%</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

n.s. = non significant

DISCUSSION

Our results show that lymphatic drainage can be visualised after local prostate treatment, making sentinel node biopsy feasible in these patients. Sentinel nodes in patients with primary tumours were mainly localized in the pelvic para-iliac area, but, in concordance to previous findings, a substantial number of these patients also had a sentinel node in an aberrant location.1-2,5-7 The lymphatic drainage pattern after treatment might be different, as suggested by the even higher number of sentinel nodes in aberrant locations in the group with recurrent prostate cancer. We have demonstrated before that sentinel nodes that are localized in aberrant locations can be tumour-positive,7,18 although in the current treated group all metastatic sentinel nodes were localized along the external iliac artery.

Studies regarding sentinel node biopsy in the previously treated breast have shown comparable findings. Several authors have concluded that sentinel node mapping is feasible after previous surgical treatment or radiation of the breast.8,9,11-15 Aberrant lymphatic drainage patterns are more frequently seen, especially after surgical treatment, but also after irradiation.8-15 The only difference is that the reported rate of non-visualisation in treated breast cancer is higher than in untreated cases,8,9,11-15 while in our population of patients with recurrent prostate cancer visualisation was good and not different from the untreated patients (100% versus 99%). The main limitation of our study is the relatively small and heterogeneous population. Therefore we cannot conclude whether different kinds of local treatment might have different effects on the lymphatic drainage of the prostate.
Levavi et al. have presented a case of vulvar carcinoma in which lymphatic mapping after chemoradiation did not reveal sentinel nodes. The authors speculate that the non-visualisation might be due to post-irradiation damage to the lymphatic channels. As initial treatment in our group was confined to the prostate only, the trauma to lymphatic channels at a distance will have been minimal. Furthermore, in our population, a mean of five years had past between the initial treatment and the local recurrence, so possibly repair and/or renewal of the lymphatic channels had occurred. These new channels might lead to nodes in aberrant locations. Although SPECT/CT can localize these nodes, intra-operative identification might be difficult due to complex anatomy. In our population, two aberrant nodes could not be found.

For oral cavity carcinoma, Wagner et al. showed that radiochemotherapy significantly influences the lymphatic drainage pattern. In this reproducibility study only six out of thirteen patients showed the same sentinel nodes before and after chemoradiation. This might imply that lymphatic mapping after the treatment does not reveal the right sentinel node anymore. Hart et al. on the other hand showed that lymphatic mapping of squamous cell carcinomas in the oral cavity or oropharynx is feasible after previous surgery or radiation therapy. They did not encounter aberrant drainage patterns. In the study one false-negative procedure occurred, but the two positive nodes were localized within the excised specimen of the primary tumour and possibly not depicted on lymphoscintigraphy due to overprojection by the injection area. In our population, we only performed lymphatic mapping after treatment and we therefore cannot compare results before and after treatment. Nodes that already contained metastases related to the first tumour might not be encountered, because lymphatic pathways may have been destroyed and renewed, leading to new sentinel nodes.

To our knowledge, we are the first to demonstrate the feasibility of sentinel node biopsy in patients with recurrent prostate cancer. Sentinel node status potentially influences treatment regimen in these patients, as it does in untreated patients. Injection into previously treated prostates might be more painful due to scar tissue. We have not specifically recorded level of discomfort during injection, but no problems have been reported and sufficient tracer uptake at the injection area was accomplished in all treated patients. The high percentage of lymphatic metastasis in patients with recurrent disease emphasizes the need for nodal staging in these patients.

An alternative to assess nodal status would be an extended lymphadenectomy. Unfortunately this procedure is associated with a substantial risk of morbidity. Furthermore, sentinel nodes might be located outside the routine template of extended pelvic lymphadenectomy and might be missed. The risk of missing such a sentinel node might be even higher if lymphatic
Lymphatic drainage from the treated versus untreated prostate

Drainage patterns have changed due to therapy. The direct draining nodes in aberrant location can be adequately localized when a sentinel node procedure includes performing a SPECT/CT. Inclusion of treated patients in larger trials might reveal the exact sensitivity and therapeutic value of sentinel lymph node mapping in recurrent prostate cancer.

CONCLUSION

Sentinel nodes in recurrent prostate cancer are more frequently found in aberrant locations, but sentinel node mapping of the treated prostate appears feasible. Large follow-up studies are necessary to establish the sensitivity and therapeutic value of lymphatic mapping in these patients.

REFERENCES


