Radionuclide-guided sentinel lymph node mapping in urachal cancer

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation;
D – writing the article; E – critical revision of the article; F – final approval of the article

Abstract

Background. Urachal cancer gives metastases through the lymph nodes (LNs). No lymphadenectomy scheme in the case of this cancer exist, yet it is proposed as a staging procedure. An assessment of lymphatic outflow from the tumor site with the use of single-photon emission computed tomography/computed tomography (SPECT/CT) lymphangiography is possible for staging purposes.

Objectives. To perform the mapping of the LNs draining the lymph from urachal cancer with the use of radioisotope-based technique and to propose the lymphadenectomy template in case of urachal cancer.

Material and methods. A prospective study was conducted in 5 patients with urachal cancer. The 99m-technetium (Tc-99m)-nanocolloid was injected during a cystoscopy prior to the surgery. Lymphangiography was performed using SPECT/CT. A radioactive LNs analysis with the use of a hand-held gamma-ray detection probe was conducted during the surgery and the sentinel lymph node (SLN) biopsy procedure was performed. An additional lymphadenectomy containing the lymphatic basin of identified radioactive LNs was performed.

Results. In all cases lymphatic outflow from the urachal tumor to the LNs was present. Preoperative SPECT/CT allowed detecting the activity of the radiotracer in the common iliac region in all the studied patients. In 3 cases, bilateral lymphatic outflow, and in 2 cases, unilateral lymphatic outflow was observed. All preoperatively visualized LNs were found and excised with the use of a gamma-ray detection probe during a lymphadenectomy. In all cases, SLNs did not contain metastases.

Conclusions. Mapping of the LNs draining the lymph from urachal cancer with the use of radiotracer is possible. Lymphatic outflow in the case of this cancer can be both unilateral and bilateral. No recommendations about the extension of lymphadenectomy are proposed. We recommend individual assessment and treatment based on additional knowledge about lymphatic outflow. This allows for minimally invasive yet targeted treatment as an SLN basin lymphadenectomy.

Key words: lymphadenectomy, urachal cancer, lymphangiography, single-photon emission computed tomography/computed tomography, dynamic sentinel lymph node biopsy
Background

The urachus is a structure measuring from 5 cm up to 10 cm that connects allantois and the bladder of the fetus. It consists of 3 layers: the luminal layer composed of cuboidal or transitional epithelium, the intermediate connective tissue, and the outer layer of smooth muscle. In the 4th to 5th month of fetus development, the bladder descends caudally, urachal lumen is stretched and then obliterated until median umbilical ligament is formed, which joins the bladder dome with the umbilicus.\(^1\) Urachal cancer is a rare non-urothelial carcinoma. Its incidence rate varies from 0.35% to 0.7% out of all bladder cancers and from 22% up to 35% of adenocarcinomas of the bladder.\(^2,3\) It is formed from the malignant transformation of enteric epithelium located in the urachus, between the bladders dome and the umbilicus. The first description of this malignancy was published in 1930 by Begg.\(^4\) There are only few case series about this neoplasm in the literature and therefore the management of each patient should be performed with an individual approach.\(^1,6,7\) This cancer is most common in men and most of the cases are in patients who are over the age of 50 years.\(^1\)

There are 5 histological subtypes of urachal carcinoma described by Grignon et al.\(^8\) The first symptom of the disease is usually hematuria, which usually occurs when the disease is already advanced. Mucosuria is another, very unusual symptom, found in 9% of patients, which indicates the possibility of urachal pathology.\(^2\) If urachal cancer is suspected, a diagnostic evaluation, physical examination and urinalysis with cytology should be performed and medical history should be taken. Cystoscopy must be performed to evaluate if the tumor penetrates the bladder urothelium and to determine the decision for a transurethral biopsy. Further diagnosis – the evaluation of the local extent, lymph node (LN) involvement and possible metastases – should consist of magnetic resonance imaging (MRI) or computed tomography (CT) of the abdomen and pelvis.

The most common metastatic sites are diagnosed in LNs, peritoneum and lungs. There are some characteristic features of the urachal tumor in imaging findings that help differentiate it from other bladder tumors. Solid urachal masses and calcification in the tumor mass as well as elevated carcinoembryonic antigen indicate urachal adenocarcinoma.\(^9\) Moreover, an elevated level of carbohydrate antigen 19-9 has been described as a tumor marker for some urachal carcinomas.\(^10\)

There are few clinicopathological criteria that can be helpful in diagnosing urachal cancer. The criteria include: tumor localized in the bladders dome, absence of cystitis cystica as well as cystica glandularis, invasion of the bladder’s muscle layer and deeper layers with a sharp margin between the healthy bladder epithelium and the tumor, its extension into the bladder wall and space of Retzius, abdominal wall or the umbilicus, the presence of urachal remnants in the tumor, and no evidence of primary neoplasm elsewhere.\(^1,4\) Not every urachal cancer is associated with the urachal remnants. Some of them develop in the presence of cystitis cystica or cystica glandularis.\(^11\) All cases diagnosed as adenocarcinoma of the bladder dome should be treated as urachal cancer until proven otherwise.\(^11\) Sheldon et al. proposed a staging system that is commonly used.\(^5\) However, several other staging systems have also been proposed.\(^12,13\)

The treatment of the urachal cancer is rather ineffective. Surgical management consisting of partial and radical cystectomy and en bloc removal of the median umbilical ligament with the umbilicus\(^14\) is the main therapeutic option. A retrospective study was performed including 40 patients with urachal adenocarcinoma where surgical treatment was associated with higher survival rates.\(^13\) When authors compared partial to total cystectomy, they observed no difference in survival between those 2 groups of patients,\(^15\) but recurrence rate after partial cystectomy was higher compared to radical cystectomy.\(^7\) Extensive tumor resection in non-metastatic patients can be curative in most cases.\(^14\) As for today, there is no evidence of the curative effect of lymphadenectomy, chemotherapy or radiotherapy.\(^4,16\) Even if the urachal cancer spreads through the LNs, no lymphadenectomy template, which should be performed during the operation, is proposed. There is also no data about the lymphatic regions where metastases are found during a lymphadenectomy. Several cases of chemotherapy treatment based on irinotecan or oxaliplatin with or without bevacizumab have been reported, as it is the first-line chemotherapy for metastatic colon cancer. This regimen was used because urachal adenocarcinomas are often histologically similar to adenocarcinomas of the gastrointestinal tract,\(^17\) but the final result of the chemotherapeutic treatment does not bring expected results.

Objectives

The goal of the present study was to assess the lymphatic outflow from the urachal cancer with the use of a radioactive tracer and mapping of first LNs draining the tumor site with the use of SPECT/CT lymphangiography. Moreover, we wanted to determine the possibility of sentinel lymph nodes (SLNs) mapping in case of urachal cancer with the use of a 99m-technetium (Tc-99m) radioisotope and compare the results of preoperative hybrid single-photon emission computed tomography/computed tomography (SPECT/CT) lymphangiography with intraoperative detection of LNs containing radioisotope with the use of a handheld gamma ray detection probe. An additional aim was to propose a scheme of individually tailored lymphadenectomy containing the SLN and its basin in case of this cancer. To our knowledge, this is the first study describing this issue.
Material and methods

Five patients with diagnosed urachal tumor were prospectively included in our study. The diagnosis of urachal cancer was based on tumor localization in cystoscopy, transurethral tumor biopsy with histopathology of adenocarcinoma, and CT scan of the pelvis and abdomen. The exclusion criteria were previous chemotherapy, pelvic radiotherapy, and previous abdominal operations. The study was approved by the local ethics committee (Independent Bioethics Committee for Scientific Research at Medical University of Gdańsk, approval No. NKBBN/522/2017-2018).

An injection of the radiocolloid was performed 1 day before the scheduled operation. The 99m-technetium-nanocolloid (Nano-Albumon; Medi-Radiopharma Kft. Érd, Hungary) was injected during the cystoscopy procedure under local anesthesia. Radiocolloid particles of 10–100 nm and the total activity of 1 mCi dissolved in 1 mL were used. The injection was performed with the use of Williams cystoscopy needle 3.7 F (Cook Urological, Spencer, USA) around the location of the tumor submucosally divided into 4 portions of 0.25 mCi per injection.

Twelve hours after the radiotracer injection, hybrid SPECT/CT lymphangiography was performed in each case with the use of the Symbia™ T6 SPECT/CT (Siemens, Erlangen, Germany) dual-head γ-camera equipped with a six-row spiral CT scanner.

The SPECT/CT acquisition parameters used during the procedure were as follows: 128 × 128 matrix, 64 frames at 30 s each, low-dose CT without an intravenous injection of contrast media. The imaging time was 30 min. Syngo software (Copyright © Siemens AG, Berlin and Munich, 2008) was used for the reconstruction and fusion of the images. Additionally, a three-dimensional (3D) reconstruction of superimposed images was performed for better visualization of the structures before the operation. Any focal activity of the radiotracer detected in the region of interest excluding the site of injection was considered to be an SLN. In each case, a partial cystectomy with en block resection of the median umbilical ligament including the umbilicus was performed. Furthermore, during the surgery radioactive LNs analysis with the use of hand-held gamma ray detection probe (Neoprobe 2000; Neoprobe Corporation) was conducted for radiotracer detection. Afterwards, dynamic sentinel lymph node biopsy (DSLNB) procedure was performed with additional lymphadenectomy containing the lymphatic basin of identified radioactive LNs. Criteria for the SLN was radioactivity at least 10 times higher than the background tissue.

Results

Clinicopathological features of the described group of patients are presented in Table 1. The mean age of patients was 64.4 years (range: 56–73 years). The study included 4 men and 1 woman. All the patients reported gross hematuria during the diagnosis; in 3 patients, irritative voiding symptoms such as urgency were present. Mucinuria was present in 3 patients. Moreover, 1 patient reported suprapubic and lumbar pain. In the course of further radiological studies, distant metastasis to the spinal cord (lumbar part) was diagnosed. In all cases, an ultrasound examination of the abdomen with a special focus on the bladder was performed (Fig. 1).

All the patients underwent a cystoscopy for the assessment of the presence of the local extension to the bladder according to the Sheldon scale (4) with tumor biopsy (Fig. 2).

Table 1. Clinicopathological features of the described group of patients

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Symptoms</th>
<th>Tumor localization</th>
<th>Tumor histology</th>
<th>Sheldon stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>gross hematuria; mucinuria, suprapubic pain; lumbar pain</td>
<td>dome</td>
<td>mucinous adenocarcinoma</td>
<td>IVB</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>gross hematuria, urgency</td>
<td>dome</td>
<td>adenocarcinoma, NOS</td>
<td>IIIA</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>gross hematuria</td>
<td>dome</td>
<td>mucinous adenocarcinoma</td>
<td>IIIA</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>gross hematuria, mucinuria, urgency</td>
<td>dome</td>
<td>mucinous adenocarcinoma</td>
<td>IIIA</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>gross hematuria, mucinuria, urgency</td>
<td>dome</td>
<td>adenocarcinoma, NOS</td>
<td>IIIC</td>
</tr>
</tbody>
</table>

M – male; F – female; NOS – not otherwise specified.
For a potential distant metastases evaluation, a contrast-enhanced CT examination of the chest, abdomen and pelvis was conducted. In 3 cases, partial cystectomy, and in 2 cases total cystectomy with umbilectomy were performed (Fig. 3–5).

In each case, the DSLNB procedure was performed with bilateral pelvic lymph node dissection (PLND) containing the basin of the SLNs. In all cases, we diagnosed the lymphatic outflow with the use of Tc-99m-nanocolloid from the urachal tumor site to the external iliac lymphatic region during preoperative SPECT/CT lymphoscintigraphy. In 3 cases – bilateral, and in 2 cases – unilateral lymphatic outflow was observed. In both cases with unilateral outflow, SLNs were located in the right iliac region. A 3D reconstruction of the images allowed for a better visualization of the position of the radioactive LNs according to the surrounding structures, which enabled a better surgeon’s preparation before the scheduled operation (Fig. 6).

All LNs preoperatively identified as SLNs on SPECT/CT were found intraoperatively with the use of hand-held gamma ray detection probe and separately excised during a lymphadenectomy for histopathologic examination. In all cases neither SLNs nor the rest of excised LNs contained metastases. The total number of excised SLNs was 8 and the total number of other removed LNs was 41 (mean: 8.2). The analysis of lymphatic outflow and excised LNs analysis is presented in Table 2.

Discussion

Urachus is an embryological remnant of the urogenital sinus and allantois. Its spontaneous closure is usually observed after forming the medium umbilical ligament as its remnant in the third trimester. In about 1/3 of adults, urachal remnants persist as a tubular or cystic structure from which cancer can develop. Morphologically, urachal
cancers are all adenocarcinomas but not all adenocarcinomas of the bladder are urachal cancers. Roughly, 10–40% of bladder adenocarcinomas are reported to be of urachal origin.\textsuperscript{1,12,19} Urachal cancer is aggressive, yet its biologic behavior presents a long and silent course. Due to its rare incidence, there is not enough literature about its treatment.

Table 2. Lymphatic outflow and lymph nodes analysis

<table>
<thead>
<tr>
<th>Case</th>
<th>Lymphatic outflow</th>
<th>SNLs localization in SPECT/CT</th>
<th>SLNs localization gamma probe intraoperatively</th>
<th>Surgery</th>
<th>Number of SNLs</th>
<th>Number of other nodes</th>
<th>SLN metastases</th>
<th>Lymph nodes metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>unilateral</td>
<td>external iliac right</td>
<td>external iliac right</td>
<td>PC + DSLNB + PLND</td>
<td>1</td>
<td>10</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>2</td>
<td>bilateral</td>
<td>common iliac right and left</td>
<td>common iliac right and left</td>
<td>TC + DSLNB + PLND</td>
<td>2</td>
<td>8</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>3</td>
<td>bilateral</td>
<td>common iliac right and left</td>
<td>common iliac right and left</td>
<td>PC + DSLNB + PLND</td>
<td>2</td>
<td>8</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>4</td>
<td>bilateral</td>
<td>external iliac right and left</td>
<td>external iliac right and left</td>
<td>TC + DSLNB + PLND</td>
<td>2</td>
<td>6</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>5</td>
<td>unilateral</td>
<td>external iliac right</td>
<td>external iliac right</td>
<td>PC + DSLNB + PLND</td>
<td>1</td>
<td>9</td>
<td>no</td>
<td>no</td>
</tr>
</tbody>
</table>

PC – partial cystectomy; TC – total cystectomy; DSLNB – dynamic sentinel lymph node biopsy; PLND – pelvic lymph node dissection; SLNs – sentinel lymph nodes.

Fig. 6. SPECT/CT lymphangiography illustrating the lymphatic outflow from the urachal cancer to the common iliac lymphatic region on the right.
and biology. There are several factors affecting the prognosis of urachal cancer. The most important ones include margin status, LN metastases, stage of the disease, distant metastases, and pathologic type. Signet ring cell adenocarcinoma as well as small cell carcinoma are the most aggressive types and cause a local invasion and dissemination even when they appear to be localized. On the other hand, mucinous adenocarcinoma has a strong tendency for a local invasion, which can result in peritoneal dissemination with a low frequency of distant metastasis. Urachal cancer is reported to have male predilection. Our study confirms this tendency, as male to female ratio was 4:1.

The prognosis for the patients with urachal cancer is poor, with five-year survival rates reported to be less than 50%. The reason for that are: late occurrence of symptoms, extravesical growth of the tumor and the risk of early metastases. A metastatic disease can be often diagnosed in case of the tumor not invading the bladder wall, diagnosed because of metastatic symptoms. Typical symptoms, such as gross hematuria and mucinuria, do not occur until the tumor invades the bladder wall. Other symptoms include dysuria, abdominal pain, suprapubic mass, and discharge of blood, pus and mucus from the umbilicus. In our study, all patients reported gross hematuria. Mucinuria as well as urgency were present in 3 cases. One patient reported lumbar pain which in further studies corresponded to the metastatic site. The most commonly described sites of distant metastases are lungs, bone with the prevalence to spine, peritoneum, LNs, and brain. In our study group, only 1 patient was diagnosed with distant metastases to the lumbar part of the spine. We have not found any metastases to the LNs. The median survival rate for patients with a metastatic disease is less than 24 months. Patients with early stage disease have a better prognosis.

Primary surgical resection in case of non-metastatic patients is recommended. It consists of a partial cystectomy and en bloc excision of the urachal tumor, urachal tract and umbilicus. In some cases, adjacent removal of organs involved with the cancer is required. Both partial and radical cystectomy provide comparable outcomes. In our group of patients, 3 underwent partial cystectomy and 2 total cystectomies because of conditions unrelated to the tumor. Survival rate is lower for patients who did not undergo umbilicectomy. What is more, authors agree that negative surgical margin status is one of the most significant predictors of prognosis.

Urachal cancer gives metastases through LNs, yet it is not clear which of them are involved in lymphatic outflow from the tumor site, how many LNs should be excised and which lymphatic regions should be excised during the lymphadenectomy procedure. What is more, lymphatic outflow from the bladder in case of bladder tumor is complicated. Both unilateral and bilateral lymphatic outflow schemes were proven. Authors also describe the position of SLNs in non-standard localizations. Other urological cancers like penile cancer often have the same tendency in lymphatic outflow. There is no data available about lateralization of the lymphatic outflow in case of urachal cancer. Moreover, distant metastases to the parotid LNs are described without pelvic LNs involvement, which can support the hypothesis about unpredictable metastatic spread.

Some authors suggest that there is no benefit in survival for patients who underwent pelvic lymphadenectomy when compared with the patients who did not undergo this procedure. Chen et al. suggested that this procedure should be performed in case of patients with LNs involvement confirmed with preoperative imaging studies. In their series, 5 out of 17 patients underwent lymphadenectomy. In 2 cases, LNs metastases were confirmed, while, in 3 cases, LNs were negative in pathological examinations. It is not clear why the authors decided to perform PLND in 5 patients while LNs metastases were present only in 2 cases in preoperative CT scans, and what radiological criteria were applied to distinguish between metastatic and non-metastatic LNs involvement. In early stages of the disease, micro-metastatic disease has to be considered. Micro-metastases are defined as measuring between 0.2 mm and 2 mm, and as for now, there is no radiological method to distinguish them from the non-metastatic LNs. When performing DSLNB for the staging purposes, we can expect to find the LNs with the most chance to acquire metastatic tumor cells from the tumor site. With the use of this technique, we can also avoid vast pelvic lymphadenectomy, which can cause side effects and may not bring additional benefits. Lymph nodes after DSLNB are also examined by a pathologist according to the SLN paragraph which differs from the standard one and which can detect a micro-metastatic disease. In our group of patients, preoperative radiological examinations did not suggest metastases to LNs. The performed SPECT/CT revealed unilateral lymphatic outflow in 2 cases and bilateral in 3 cases. No metastases to SLNs nor metastatic cells were found in the rest of the excised LNs.

It is still debatable whether to routinely perform a bilateral lymphadenectomy in patients qualified for surgical treatment because of urachal cancer. The procedure may be challenging and cause postsurgical complications, but on the other hand, omitting lymphadenectomy results in the lack of information about the stage of the disease. This can have a significant effect on the course of the adjuvant treatment.

Patients with a metastatic disease can be treated effectively with systemic chemotherapy, but as for now, no standard chemotherapeutic regimen is proposed. Various chemotherapeutics have been used with different treatment results. Chemotherapeutics used for bladder cancer based on cisplatin were used in patients with urachal cancer, with limited clinical effect. Other regiments including 5-fluorouracil (5-FU) were expected to be efficient because of the histological and clinical similarities of urachal to colonic adenocarcinoma. While comparing..
studies with the use of cisplatin-based, 5-FU-based and combined cisplatin + 5-FU-based regimens, the highest response rate and lowest progression was observed in case of the use of combined regimen. Other authors suggest the usage of neoadjuvant gemcitabine + cisplatin (GC) and subsequently l-leucovorin + 5-FU + irinotecan (FOLFIRI) regimen for mucinous adenocarcinoma, aiming at tumor shrinkage allowing the curative surgery. Our primary results can be used as a recommendation to perform an individual assessment of patients with urachal cancer and perform targeted lymphadenectomy containing the SLN and its basin, depending on the results of preoperative SPECT/CT lymphoscintigraphy. In case of a metastatic disease to the LNs and distant metastases, adjuvant chemotherapy should be implemented. In our group of patients, we did not find a micro-metastatic disease while performing pathological examination on SLNs, so no recommendations in that case can be presented.

Conclusions

Urachal cancer gives metastases through the LNs. In case of this cancer, no lymphadenectomy scheme is proposed, and no range of the lymphatic tissue excision is accepted as a standard. In case of urachal cancer, lymphadenectomy is performed as a staging procedure, but it does not bring any benefit for the patient’s survival. Its performance can lead to adverse events and complications during and after the surgery, like lymphoedema and lymphocele.

An assessment of the lymphatic outflow from the urachal cancer with the use of radioactive tracer and mapping of first LNs draining the tumor site is possible. An assessment of lymphatic outflow from the tumor site with the use of SPECT/CT lymphangiography is feasible and gives additional information to the surgeon, allowing for a better planning of the operation.

Lymphatic outflow from the injection site around the urachal cancer can be unilateral and bilateral. The DSLNB in case of urachal cancer with the use of intraoperative gamma ray detection probe is possible. A combination of both techniques — preoperative SPECT/CT lymphangiography with 3D images reconstruction and an intraoperative gamma ray detection probe — allows the surgeon for an excellent estimation of the localization of radioactive LNs.

Since no recommendations about the extension of lymphadenectomy are proposed, we recommend an individual assessment of each patient and treatment based on additional knowledge about the lymphatic outflow. This allows for a minimally invasive yet targeted treatment as an SLN basin lymphadenectomy. This technique can spare the performance of a bilateral pelvic lymphadenectomy in case of unilateral lymphatic outflow.

Further studies on a larger group of patients are needed for a better lymphatic outflow assessment in case of this cancer.