

Accepted Manuscript

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PII: S1558-7673(16)30163-X

DOI: [10.1016/j.clgc.2016.06.012](https://doi.org/10.1016/j.clgc.2016.06.012)

Reference: CLGC 641

To appear in: *Clinical Genitourinary Cancer*

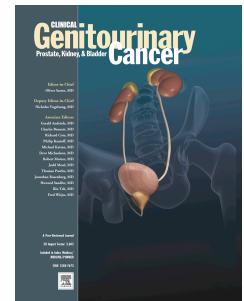
Received Date: 5 April 2016

Revised Date: 23 May 2016

Accepted Date: 11 June 2016

Please cite this article as: Khetrpal P, Shen TW, Lamb B, Nathan S, Briggs T, Shankar A, Ramachandran N, Freeman A, Mitra A, Kelly JD, Port-site metastases following robotic radical cystectomy: A systematic review and management options, *Clinical Genitourinary Cancer* (2016), doi: [10.1016/j.clgc.2016.06.012](https://doi.org/10.1016/j.clgc.2016.06.012).

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Port-site metastases following robotic radical cystectomy: A systematic review and management options.

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Abstract

Background: Port-site metastases (PSM) are a rare occurrence in robotic surgery. For robot assisted radical cystectomy (RARC), isolated cases have been reported but management has not been described previously. We present a case of PSM that occurred after RARC and perform the results of our systematic review of previously reported port site metastases, and describe treatment options.

Methods: We describe a case of a PSM in a 55-year old gentleman who underwent intracorporeal RARC. We performed a systematic review of MEDLINE and EMBASE databases for previously reported PSMs, detailing the stage and grade of the primary tumour, time to presentation of PSM, treatment offered and outcomes for the identified cases.

Results: We identified four cases of PSMs following RARC in the literature, and included our case for analysis. All five cases had muscle invasive bladder cancer at time of cystectomy ($>T2$) and three of them had local lymph node positive disease. Our aggressive treatment of chemotherapy, wide surgical excision of PSM and radiotherapy has provided the patient a two-year disease-free status.

Conclusion: PSMs are a rare event in RARC, with only four other cases described in the literature. Outcomes have are not well reported for all of these cases, and we propose that a multi-modality treatment consisting of salvage chemotherapy, surgery and radiotherapy should be considered, but concessions have to be made taking patient factors into account.

Background:

Port-site metastases (PSM) are a rare complication of minimally invasive surgery. Micali et al., reported an incidence of 0.09% (10 PSM in 10,912 cases) following a survey of urology procedures carried out for cancer.¹ Minimally invasive radical cystectomy is a relatively new procedure evidenced by inclusion of only 95 cases in the series by Micali et al.¹ Despite few large case series, isolated PSMs have been reported.² Urothelial cell carcinoma is chemotherapy and radiotherapy sensitive^{3,4}, and more recent reports that targeting the immune response improves survival in the advanced and metastatic setting⁵, points to a role for multimodality therapy in the management of PSM following cystectomy. Herein we describe the incidence of PSM based on a systematic review and set out management options our experience in relation to robotic cystectomy.

Case:

A 55-year-old male underwent radical robotic cystoprostatectomy and intracorporeal ileal conduit formation (iRARC) for poorly differentiated muscle invasive urothelial cell carcinoma. The resected specimens were removed from the port placed 5 cm above and lateral to the right and left anterior superior iliac spine in an Endo Catch™ Specimen Pouch (Covidien, Dublin, Ireland). The tumour was causing high-grade obstruction of the vesicoureteric junction, resulting in moderate right sided hydronephrosis and a reduced pre-operative eGFR, which precluded neo-adjuvant chemotherapy. His post-operative recovery was uneventful other than a suprapubic insertion site wound infection requiring co-amoxiclav (classified as a Clavien Dindo grade II)⁶. Histopathological assessment confirmed poorly differentiated Grade III urothelial cell with microscopic extension into perivesical fat. The surgical margin was clear and eighteen removed nodes were all negative (pT3aN0).

Two months after surgery, the patient developed tenderness over the left lower anterior abdominal wall. Examination revealed a 7cm x 3 cm mobile mass related to the left iliac fossa port site. MRI confirmed two discrete, partially enhancing lesions within the abdominal wall musculature at the left iliac fossa (Image 1). CT imaging excluded other metastatic disease; and PET CT imaging (Image 2a) confirmed avid tracer uptake establishing a diagnosis of isolated metastatic disease. A biopsy was not performed and the consensus opinion from a multidisciplinary team meeting (MDT) was for multimodal therapy based on clinical and radiological findings. Treatment consisted of 3 cycles of gemcitabine and cisplatin, and interval imaging showed partial response (Image 2b) after the 3 cycles of chemotherapy had been administered. The patient was re-discussed at MDT and a planned wide surgical excision of the PSM and mesh reconstruction was performed 5 weeks after completion of chemotherapy. At operation, the location of the mass was confirmed within the transverse abdominal and internal oblique muscles. The mass penetrated to the peritoneal surface with adherence of sigmoid epiploica at this point. A partial sigmoid resection was performed to achieve wide cancer clearance, the left iliac crest limited the distal excision and reconstruction of the abdominal wall with Strattice™ Reconstructive Tissue Matrix (LifeCell, New Jersey, USA) was

necessary. Histology confirmed a 40 x 30 mm tumour. The tumour was 4 mm from the iliac resection margin. Subcutaneous tissue and bundles of striated muscle contained poorly differentiated urothelial cell carcinoma. Following surgical excision, post-operative external beam radiotherapy was commenced (week 4) and 45Gy in 25 fractions over 5 weeks with 6MV photons was delivered using a conformally planned technique.

Surveillance by CT imaging, initially at 3 monthly intervals extending to 6 months after 1 year was instituted and at 2 years from surgery the patient is recurrence free.

Search criteria and methods:

A literature search was performed using MEDLINE and EMBASE for the following MESH terms: 'cystectomy' and 'robotic' in the abstract. Articles were excluded if there were no cases of PSM, duplicate reports, reviews or letters to the editor. Only articles in English were included. 1496 articles matched the search criteria, and 372 duplicates were identified and 30 results were non-English records. Abstracts and full texts of the remaining 1094 articles were manually reviewed for reports of PSM occurring post-robotic cystectomy.

Results:

Four cases describing the occurrence of PSM were identified in patients who underwent RARC for bladder cancer.^{2,7,8,9} Three of the cases were reported as part of the International Robotic Cystectomy Consortium (IRCC) database which collects data from 37 global institutions and holds 1,586 consecutive cases.⁹ A fourth case was reported by El-Tabey et al., in a series of 17 cases and, we report one occurrence of PSM in our experience of 173 cases as of March 2016. From these figures, the incidence of PSM following robotic cystectomy for bladder cancer is currently estimated at between 0.2-0.3%.

Consistent with the case described, all PSM have been associated with muscle-invasive disease, locally advanced and, or lymph node positive disease. The time to recurrence varies between 2 and 10 months from RARC.⁷ An aggressive multimodal management was pursued for the case which we describe following a similar planned approach described by El-Tabey.⁷ There is no information about treatment offered in relation to the remaining cases. This data is summarised in Table 1, along with the case described in this report.

Discussion:

The incidence of PSM following RARC of less than 0.5% is greater than for combined genitourinary cancers (0.09%), laparoscopic prostate cancer surgery (0.1%)¹⁰ and laparoscopic radical nephrectomy 0.1%.¹ The incidence of PSM following cystectomy is lower than for robotic gynaecological procedures for various cancers (endometrial, cervical, ovarian, fallopian tube) at between 1.1 and 1.9%.^{11,12} Given the relatively low number of case series reported, the

incidence for PSM following cystectomy can be considered an estimate and may alter in time. The incidence of incision site metastases after open radical cystectomy is not well described and may be under-reported. In a series of 100 consecutive open radical cystectomy cases, we reported a single case of umbilical site recurrence.¹³

The presumed mechanism for the development of PSM is tumour implantation caused by cancer cell contamination and the reports of cystectomy PSM occurring in advanced stage and poorly differentiated disease is consistent with tumour spillage. Contributing plausible factors are seeding during extraction of the tumor, contact with contaminated laparoscopic instruments, and the effects of pneumoperitoneal desufflation.^{14–16} Although it is postulated that PSM can be a result of haematogenic or lymphogenic spread, studies in animal models have failed to support this; in colorectal cancer haematogenic spread to the liver and lungs precedes other sites.¹⁷ In bladder cancer, PSMs have been described as an initial or isolated event supporting tumour implantation as the main causal factor.

In the absence of guidelines and reported outcomes following treatment, after exclusion of other local or metastatic disease, we pursued an aggressive multimodal therapy plan and we acknowledge that decision to treat must be made on a case-by-case basis. As the aetiology of PSM is likely to be related to mechanical disease dissemination during surgery, aggressive multi-modal treatment may offer affected patients a tumour-free outcome consistent with the 5 year cancer-free survival for local advanced and node positive disease of between 89% and 29%.¹⁸ We were unable to find best practice guidance for the management of PSM in other cancers. A systematic review of PSM in robotic-assisted gynaecological procedures for cancer outlined the management of 20 cases including combinations of surgical excision, chemotherapy and radiotherapy, with surgery alone being the commonest (9/20) and 3 patients receiving all three modalities of treatment although long-term cancer specific survival was not reported.¹⁹ Benefit from neo-adjuvant chemotherapy in the management of muscle-invasive bladder cancer is well-established and incorporated in current guidelines as is the benefit in the adjuvant setting.^{20–22} In addition, outcomes for radiotherapy showing a reduction in local and regional recurrence²³ have been encouraging and support the multi-modality approach. Furthermore, recent evidence showing benefit for immunomodulation using MPDL3280A, an anti-PD-L1 antibody in advanced metastatic bladder cancer may extend the therapy options.⁵

For the case described herein, the surgical plan considered inserting a spacer after resection of the port-site metastases to increase the distance between bowel and the radiotherapy target site minimising toxicity. This was not possible after resecting the tumour mass and sigmoid colon but remains an option to consider in future cases. A further consideration is the abdominal wall reconstruction following a wide local excision and in the case described, despite acellular tissue matrix mesh reconstruction, a hernia developed with necessity for subsequent reconstruction.

3660 Da Vinci consoles are currently installed in the world, with 2431 in the United states, 616 in Europe, 441 in Asia and 172 in the rest of the world.¹ A recent survey by Hu et al. compared RARC (n = 439) vs ORC (n = 7308) and found that while inpatient costs were similar, higher 30-day and 90-day costs were identified, with higher home health care being utilised.²⁴ Bochner et al compared RARC (n = 60) vs ORC (n = 58) in an randomised control trial

Conclusion:

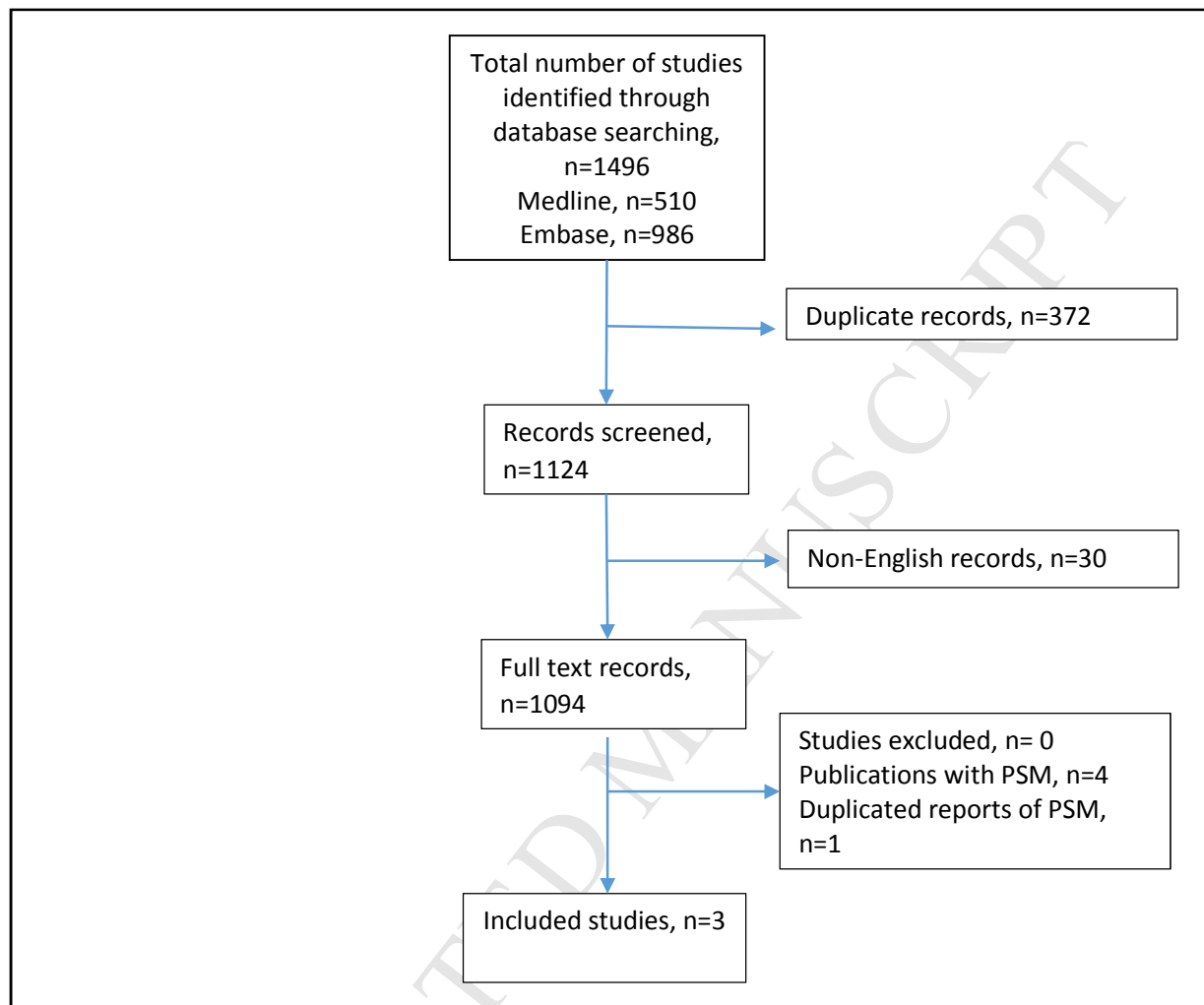
The incidence of PSM following robotic radical cystectomy for bladder cancer is low (<0.5%) but greater than other genitourinary malignancies. PSMs are more likely in the following surgery for locally advanced and node positive disease and careful attention during extraction is an important and obvious preventative step. In selected cases, in the absence of other local and metastatic disease a multimodal treatment strategy involving salvage chemotherapy, surgery and radiotherapy should be recommended.

Conflict of Interest

The authors have no conflict of interest to disclose.

¹ <http://phx.corporate-ir.net/phoenix.zhtml?c=122359&p=irol-faq>

174 **Figures, tables and images:**



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176 Figure 1: Search strategy and results for literature search

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| Case No | Author | Tumour stage & grade | Time to presentation | Treatment | Outcome |
|---------|---|----------------------|----------------------|---|-------------------------|
| 1 | El-Tabey 2005 ⁷ | T3bN0M0 G3 | 10 months | Offered local excision, radiotherapy and/or chemotherapy. | Not stated |
| 2 | Saar, 2014 ⁹ | T>2N1M0 | - | Not stated | Not stated |
| 3 | Saar, 2014 ⁹ , Raza, 2015 ² | T>2N1M0 | 3 months | Not stated | Not stated |
| 4 | Saar, 2014 ⁹ | T>2N1M0 | - | Not stated | Not stated |
| 5 | Khetrapal | T3N0M0 G3 | 2 months | Neoadjuvant chemotherapy, excision, adjuvant radiotherapy | Disease-free at 2 years |

Table 1: Cancer staging and outcomes for individual cases of port-site metastases.



Image 1: CT of the abdomen showing the port-site metastases in the transverse abdominal and internal oblique muscles.

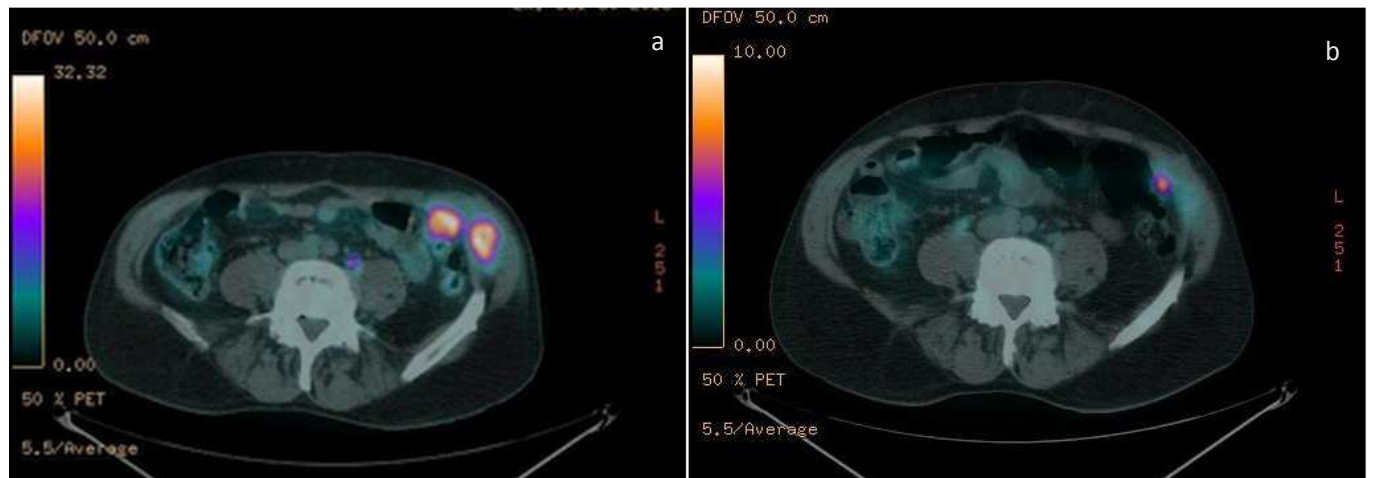


Image 2: CT PET showing PET avid uptake within the abdominal wall musculature pre-chemotherapy (a) and 3 weeks after 3rd cycle post chemotherapy (b) showing partial response to neo-adjuvant gemcitabine and cisplatin chemotherapy.

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