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

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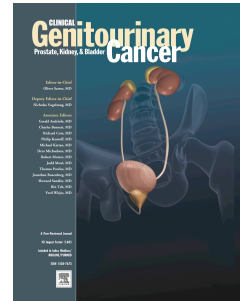
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1 **Port-site metastases following robotic radical cystectomy: A systematic review**
2 **and management options.**

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25 **Abstract**

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

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

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

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

44 Background:

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

55 Case:

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

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

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

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

90 **Search criteria and methods:**

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

97

98 **Results:**

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

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

112

113 **Discussion:**

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

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

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

132 In the absence of guidelines and reported outcomes following treatment, after exclusion of
133 other local or metastatic disease, we pursued an aggressive multimodal therapy plan and we
134 acknowledge that decision to treat must be made on a case-by-case basis. As the aetiology of
135 PSM is likely to be related to mechanical disease dissemination during surgery, aggressive
136 multi-modal treatment may offer affected patients a tumour-free outcome consistent with the
137 5 year cancer-free survival for local advanced and node positive disease of between 89% and
138 29%.¹⁸ We were unable to find best practice guidance for the management of PSM in other
139 cancers. A systematic review of PSM in robotic-assisted gynaecological procedures for cancer
140 outlined the management of 20 cases including combinations of surgical excision,
141 chemotherapy and radiotherapy, with surgery alone being the commonest (9/20) and 3
142 patients receiving all three modalities of treatment although long-term cancer specific survival
143 was not reported.¹⁹ Benefit from neo-adjuvant chemotherapy in the management of muscle-
144 invasive bladder cancer is well-established and incorporated in current guidelines as is the
145 benefit in the adjuvant setting.²⁰⁻²² In addition, outcomes for radiotherapy showing a reduction
146 in local and regional recurrence²³ have been encouraging and support the multi-modality
147 approach. Furthermore, recent evidence showing benefit for immunomodulation using
148 MPDL3280A, an anti-PD-L1 antibody in advanced metastatic bladder cancer may extend the
149 therapy options.⁵

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

157 3660 Da Vinci consoles are currently installed in the world, with 2431 in the United states, 616
158 in Europe, 441 in Asia and 172 in the rest of the world.¹ A recent survey by Hu et al. compared
159 RARC (n = 439) vs ORC (n = 7308) and found that while inpatient costs were similar, higher 30-
160 day and 90-day costs were identified, with higher home health care being utilised.²⁴ Bochner et
161 al compared RARC (n = 60) vs ORC (n = 58) in an randomised control trial

162

163 **Conclusion:**

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

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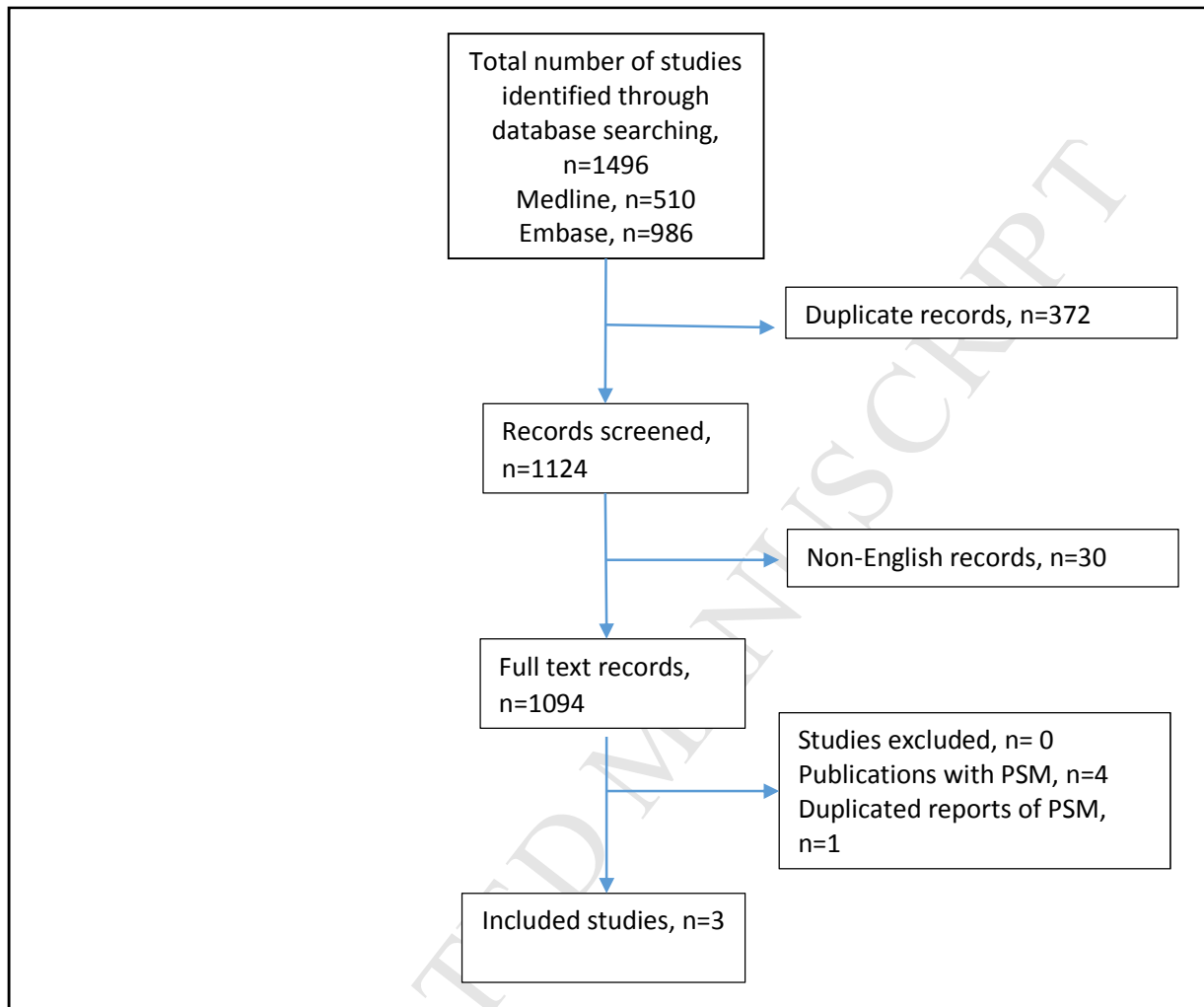
171 **Conflict of Interest**

172 The authors have no conflict of interest to disclose.

173

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

174 **Figures, tables and images:**



175

176 Figure 1: Search strategy and results for literature search

177

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

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

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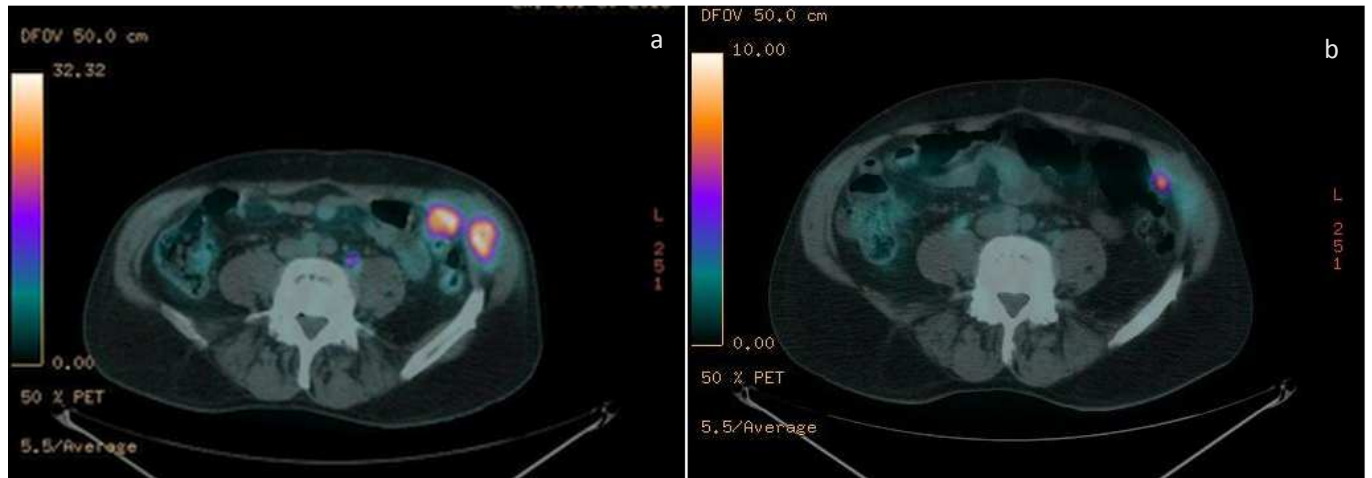
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194 Image 1: CT of the abdomen showing the port-site metastases in the transverse abdominal and internal
195 oblique muscles.



196

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

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