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Title: Long-term survival in a patient with abdominal sarcomatosis from uterine leiomyosarcoma: role of repeated laparoscopic surgery in the treatment and follow-up

Article Type: Case Report

Keywords: abdominal sarcomatosis, leiomyosarcoma, laparoscopy, quality of life

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Abstract: Uterine leiomyosarcoma (LMS) in some cases may disseminate through the abdominal cavity, without extra-abdominal spreading, determining a condition of abdominal sarcomatosis, which represents a peculiar situation. Only radical surgical removal offers a chance of long-term survival in such cases of LMS. In the present paper, we describe an emblematic case of diffuse AS from uterine LMS in a 51-year-old perimenopausal woman who underwent laparoscopic radical hysterectomy, bilateral salpingo-oophorectomy, total pelvic peritonectomy, pelvic lymphadenectomy to the mesenteric inferior artery, and omentectomy. Then, given the high probability of disease recurrence, the patients underwent a close follow up consisting of positron emission tomography (PET)/computed tomography (CT) every 3 months and diagnostic (and if necessary operative) laparoscopy every 6 months. To date the patient had 11 laparoscopies; five of them preceded by a PET indicative of the presence of disease with high metabolic activity, which was confirmed at surgery and each time completely removed laparoscopically with no evidence of residual disease. To date, after 5 years from diagnosis the patient is alive and continues her follow-up. Our report brings to light the ability of laparoscopic surgery to obtain a disease control in case of LMS with abdominal dissemination. Moreover, laparoscopic surgery, as demonstrated in our case, may have an important role in the close follow-up of the disease and allow a timely and early radical surgical approach of relapses before they become extremely large and difficult to remove radically.

Cagliari, 11 April 2016

Editor-in-Chief
Journal of Minimally Invasive Gynecology

Dear Editor-in-Chief

It is a pleasure to submit for consideration the following manuscript entitled “Long-term survival in a patient with abdominal sarcomatosis from uterine leiomyosarcoma: role of repeated laparoscopic surgery in the treatment and follow-up” for publication in your prestigious journal *Journal of Minimally Invasive Gynecology* as case report.

Uterine leiomyosarcoma in some cases may disseminate through the abdominal cavity, without extra-abdominal spreading, determining a peculiar condition of abdominal sarcomatosis. Only radical surgical removal offers a chance of long-term survival in such cases of leiomyosarcoma. In the present paper, we describe a case of diffuse abdominal sarcomatosis from uterine leiomyosarcoma who underwent laparoscopic radical hysterectomy, bilateral salpingo-oophorectomy, total pelvic peritonectomy, pelvic lymphadenectomy to the mesenteric inferior artery, and omentectomy. Considering the high risk of relapse, the patients underwent a close follow up consisting of positron emission tomography/computed tomography and diagnostic/laparoscopy every 6 months. To date the patient had 11 laparoscopies; five of them preceded by a positron emission tomography indicative of the presence of disease with high metabolic activity, which was confirmed at surgery and each time completely removed laparoscopically with no evidence of residual disease. After 5 years from diagnosis the patient is alive and continues her follow-up.

Our case supports the ability of laparoscopic surgery to obtain a disease control in case of leiomyosarcoma with abdominal dissemination, and demonstrated that laparoscopic surgery may have an important role in the close follow-up of the disease and allow a timely and early radical surgical approach of relapsed disease.

To our knowledge, our paper is the first that describes such successful use of a repeated laparoscopic approach of abdominal sarcomatosis from uterine leiomyosarcoma associated with a long-term survival.

We believe that the findings of this study are relevant to the scope of your journal and will be of interest to its readership.

This manuscript has not been published or presented elsewhere in part or in entirety, and is not under consideration by any other journal. The patients provided written consent for publication of the report. All the authors have approved the manuscript and agree with submission to your esteemed journal. There are no conflicts of interest to declare.

Thank you for your consideration.

Sincerely,
Antonio Macciò

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Precis

In the present paper we describe an emblematic case of a long-term surviving patient with diffuse abdominal sarcomatosis from uterine LMS treated with a repeated radical laparoscopic approach.

1 **Long-term survival in a patient with abdominal sarcomatosis from uterine leiomyosarcoma:**
2 **role of repeated laparoscopic surgery in the treatment and follow-up.**

3

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21 **Conflict of interest:** There are no conflicts of interest to declare.

22

23 **Abstract**

24 Uterine leiomyosarcoma (LMS) in some cases may disseminate through the abdominal cavity,
25 without extra-abdominal spreading, determining a condition of abdominal sarcomatosis, which
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27 in such cases of LMS. In the present paper, we describe an emblematic case of diffuse AS from
28 uterine LMS in a 51-year-old perimenopausal woman who underwent laparoscopic radical
29 hysterectomy, bilateral salpingo-oophorectomy, total pelvic peritonectomy, pelvic
30 lymphadenectomy to the mesenteric inferior artery, and omentectomy. Then, given the high
31 probability of disease recurrence, the patients underwent a close follow up consisting of positron
32 emission tomography (PET)/computed tomography (CT) every 3 months and diagnostic (and if
33 necessary operative) laparoscopy every 6 months. To date the patient had 11 laparoscopies; five of
34 them preceded by a PET indicative of the presence of disease with high metabolic activity, which
35 was confirmed at surgery and each time completely removed laparoscopically with no evidence of
36 residual disease. To date, after 5 years from diagnosis the patient is alive and continues her follow-
37 up. Our report brings to light the ability of laparoscopic surgery to obtain a disease control in case
38 of LMS with abdominal dissemination. Moreover, laparoscopic surgery, as demonstrated in our
39 case, may have an important role in the close follow-up of the disease and allow a timely and early
40 radical surgical approach of relapses before they become extremely large and difficult to remove
41 radically.

42

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44 **Key words:** abdominal sarcomatosis, leiomyosarcoma, laparoscopy, quality of life

45

46 **Introduction**

47 The dissemination of soft tissue sarcoma all over the abdominal cavity without extra-abdominal
48 spread is known as abdominal sarcomatosis (AS), an uncommon disease most often arising from
49 uterine leiomyosarcoma (LMS) [1]. Although the majority of uterine LMS are confined to the
50 uterus, many cases involve local spread to peritoneal surfaces and adjacent organs and distant
51 metastasis [2]. Tumor stage is the strongest prognostic factor for all uterine sarcomas, with a 5-year
52 survival rate of 50–55% for stage I patients, and 8–12% for patients with more advanced tumors [3].
53 The current management of uterine LMS does not take into account individual clinical pathologic
54 prognostic factors, such as tumor size (>5 or ≤ 5 cm), mitotic activity (≤ 10 or >10 mitosis/10 high-
55 power fields [HPFs]), age, and vascular invasion [3]. In view of this evidence, the prognosis of
56 peritoneal sarcomatosis cannot be well established. Only radical surgical removal offers a chance of
57 long-term survival in cases of LMS [4]. In this context, AS associated with primary uterine LMS
58 represents an unusual situation. There are also growing cases involving peritoneal sarcomatosis
59 from occult uterine LMS following the use of internal morcellation for laparoscopic hysterectomies,
60 or myomectomy for presumed uterine fibroids [5,6]. The management of AS from uterine LMS is
61 therefore difficult as optimal radical resection may be complicated by disease spread and frequent
62 recurrence and very few data are available about a laparoscopic approach. To date, conventional
63 therapeutic modalities have failed to improve the outcome of patients with uterine LMS associated
64 with extrapelvic spread. Retrospective analyses [7-10] and phase II studies [11,12] analyzed the
65 morbidity and mortality of cytoreductive surgery (CRS) and hyperthermic intraperitoneal
66 chemotherapy perfusion (HIPEC) in the treatment of uterine LMS with abdominal spread. The lack
67 of effective chemotherapeutic agents coupled with the hematogenous spread of sarcomas means that
68 the use of CRS-HIPEC remains controversial [1,13]. Furthermore, some authors found no
69 difference between patients treated with or without HIPEC after complete cytoreduction, suggesting
70 that resection status is more important for survival than HIPEC use [10,13]. These discordant results
71 may reflect large variations in the behavior of these tumors, and their best definition is mandatory.

72 In this context, we describe one emblematic clinical case of diffuse AS from uterine LMS, with a
73 long survival obtained through repeated cytoreductive laparoscopic surgeries. The description of
74 this case may contribute to clarify the central role of surgery, and in particular of a laparoscopic
75 approach, in the treatment of this disease and implement our knowledge of their biological
76 heterogeneity, which may have therapeutic implications.

77

78

79 **Case report**

80 Written informed consent was obtained from the patient for publication of the case report and
81 accompanying images. The retrospective observational nature of the study did not necessitate the
82 local institutional ethics committee approval.

83 Five years ago, a 51-year-old perimenopausal pluriparous (gravida 2 and para 2) Caucasian woman
84 who was not taking oral contraceptives presented with menometrorrhagia. Physical examination
85 revealed an enlarged uterus that was thought to be a result of uterine fibromatosis with multiple
86 myomas. Abdominal ultrasonography (US) confirmed an enlarged uterus deformed by the presence
87 of probable multiple myomas. Serum CA-125 levels were 75 U/mL (normal range <34 U/ml). For
88 this reason, we performed laparoscopy to examine the uterus and help determine the most suitable
89 surgical approach. In reason of the large volume of the uterus, a port was placed above the
90 umbilicus and a pneumoperitoneum of 14 mmHg was established and maintained throughout the
91 surgery. Intra-abdominal visualization was achieved using a 10 mm, 0° telescope (Karl Storz,
92 Tuttlingen, Germany) and three 5-mm trocars were introduced under laparoscopic visualization
93 through ports in each lower quadrant and in the suprapubic region. Our initial observation showed a
94 greatly enlarged uterus, deformed by numerous reddish-brown nodules in its anterior and posterior
95 walls. These neoformations also extended throughout the pelvic peritoneum (Douglas's cavity,
96 vesicouterine recess, and right pararectal lodge), the great omentum, the mesosigma, the small
97 intestine mesenterium, and the abdominal peritoneum (Figure 1). Extemporaneous examination

98 revealed a mesenchymal neoplasm with signs of atypia compatible with sarcoma. Laparoscopic
99 surgery was considered possible, and a radical laparoscopic hysterectomy, bilateral salpingo-
100 oophorectomy, total pelvic peritonectomy, pelvic lymphadenectomy to the mesenteric inferior
101 artery, and omentectomy were performed. The disseminated nodules could be easily resected
102 because they had not infiltrated the surrounding tissue. Each of the resected nodule fragments and
103 the lymph nodes were collected in several 10 cm endobags and removed vaginally as well as the
104 omentum. Uterus was removed in accordance with the bowel bag technique developed by Heaton
105 for pelvic mass isolation (14). After the radical hysterectomy, with the uterus intact, a bowel bag
106 was inserted into the abdomen via the vagina, and the uterus was maneuvered into it. The bag
107 mouth was then brought out through the vagina, and the uterus was morcellated inside the bag to
108 prevent intra-abdominal contamination. The surgery lasted for 4 hours and it apparently achieved a
109 complete cytoreduction; and the patient was discharged in good condition after 48 hours.

110 Pathological examination revealed a uterus weighing 515 grams deformed by various formations
111 similar to myoma nodes, and 15 irregular nodular neoforations from the abdominal cavity
112 (diameter ranging from 0.5 to 6 cm). There were also several nodules with a diameter ranging from
113 0.5 to 3 cm in the omentum. Definitive histopathological examination revealed that all of these
114 samples were high-grade uterine LMSs with a high mitotic index (43 mitosis/10 HPF), and a Ki-67
115 of 30%. A LMS was also localized to the right perituberic space. The adnexa and fallopian tubes
116 were normal, and 36 resected lymph nodes were free of neoplastic involvement.

117 After a thorough bibliographic examination, the patient was interviewed to schedule the most
118 appropriate follow-up and to discuss potential adjuvant therapy. The efficacy of systemic adjuvant
119 therapy (15) and intraperitoneal hyperthermia is unclear, and there is no evidence for an absolute
120 benefit of adjuvant therapy compared with surgery alone (16,17,18). Therefore, with the patient's
121 agreement, given the high probability of disease recurrence, we decided on a follow up consisting
122 of positron emission tomography (PET)/computed tomography (CT) every 3 months, which, if
123 positive, would be accompanied by a diagnostic (and if necessary operative) laparoscopy. A

124 diagnostic laparoscopy was planned every 6 months, even in absence of PET positivity, considering
125 such approach the most appropriate way to obtain the closest monitoring useful for the control of
126 this insidious disease. At the time of reporting, 11 laparoscopies have been performed; five of them
127 were preceded by a PET suggesting the presence of disease with high metabolic activity, which was
128 then confirmed at surgery and each time completely removed laparoscopically with no evidence of
129 residual disease. Figure 2 show laparoscopic visualization of multiple peritoneal localization of
130 relapsed LMS. In particular, in the 10th re-intervention the presence of two metastases infiltrating
131 the small intestine (Figure 3) has made it indispensable to perform the laparoscopic resection of the
132 interested intestinal tract. The video (supplemental material) shows the laparoscopic removal of the
133 peritoneal localizations corresponding to the PET/CT images of the multicentric peritoneal nodule
134 localized at the level of the right common iliac artery (Figure 4).

135 Surgeries lasted for 90 minutes on average (range 45-120). No bleeding occurred, and the patient
136 was discharged within 48 hours after each surgery, except after the intestinal resection that required
137 a discharge after 5 days. The quality of life (QL) assessment after each intervention showed an
138 excellent performance status. After each surgery, an interview with the patient confirmed the
139 treatment choice. The patient currently wishes to continue with this approach, and at to date she is
140 under planned follow up.

141

142

143 **Comment**

144 The clinical course of patients with uterine LMS is difficult to predict with the currently available
145 modified categorical staging system of the International Federation of Gynecology and Obstetrics
146 (FIGO) [3, 19], especially when an AS is associated with it. AS is defined as the intra-abdominal
147 dissemination of sarcoma and may be present at initial diagnosis, but is also frequently observed at
148 recurrence, presumably because of tumor spillage during the initial resection [1]. Recently, a new
149 category of AS has been observed following uterine morcellation during laparoscopic subtotal

150 hysterectomy, laparotomy, or laparoscopic myomectomy for occult LMS [20-22]. This point makes
151 yet unclear the role of laparoscopic surgery in the management of these tumors.

152 Indeed, despite the FIGO staging indications, in which AS should be a negative prognostic factor,
153 the growth of massive intra-abdominal sarcomatoid masses in the absence of distant metastases may
154 be a potentially favorable prognostic finding in some cases. These clinical pictures illustrate the
155 lack of a strong relationship between clinical staging and prognosis, and highlight the importance of
156 basing treatment decisions on the tumor biological characteristics rather than its stage.

157 The abdominal spread of LMS could indicate either a particularly rapid increase in size facilitated
158 by the space available in the abdominal cavity rather than a tendency to metastasize to distant sites,
159 or the development of a multicentric disease, as observed in cases of abdominal benign diffuse
160 leiomyomatosis [23]. The lack of infiltrating capacity of some of these tumors and the fact that they
161 can be easily dissected, as showed by us, support this hypothesis, opening in these isolated cases
162 new perspectives on the use of laparoscopic surgery to safeguard the best QL. Indeed, this evidence
163 argues also that we are facing with tumors with a peculiar neoplastic behavior. Therefore, more
164 complex post-surgical staging systems that can facilitate the best therapeutic choice are needed. In
165 addition to stage, other prognostic factors in uterine LMS should include age, grade, tumor size,
166 mitotic rate, DNA ploidy, and menopausal status, none of which are incorporated into the FIGO
167 staging system [24]. Indeed, the American Joint Committee on Cancer uses a separate staging
168 system specifically for soft tissue sarcomas that, among other variables, includes tumor size and
169 grade [25]. Neither of these two staging systems assesses the tumor size and local spread in addition
170 to their infiltrating and distant metastatic ability. This is important because, as surgery is the
171 mainstay therapy for these tumors, the best definition of the disease would help to avoid to selected
172 patients adjuvant chemotherapy, which has uncertain efficacy and is associated with adverse effects
173 that can severely affect the patient's QL.

174 Supporting this observation, another point to be discussed is the role of the most appropriate
175 imaging technique able to identify the recurrence in order to plan an early and more effective

176 surgical approach. In this context some studies have demonstrated that the PET/CT is a highly
177 sensitive and specific modality for detecting recurrence in post-therapy patients with LMS (26,27).
178 Moreover, the peritoneal metastases, especially those localized between the short bowel intestinal
179 loops, cannot be easily identified with CT. Vice versa, PET/CT can identify the metabolic activity
180 of such lesions and therefore give information about their presence.

181 In conclusion, only recently, evidence support also a role of laparoscopic surgery for the treatment
182 of early stage uterine sarcomas (28). A laparoscopic approach as described in the present case can
183 be pursued only in centers with great expertise with laparoscopic hysterectomy (29).

184 A new approach along these lines could offer an extended role for laparoscopy in the management
185 of abdominal LMS, as demonstrated by our case, respecting the best patient's QL. This, in turn,
186 would allow a timely and early surgical approach before they become extremely large. Further
187 evidence is needed to better standardize this approach.

188

189

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271 **Figure legend**

272 **Figure 1.** Laparoscopic visualization of the uterus and multiple peritoneal pelvic metastatic
273 localizations of leiomyosarcoma at diagnosis.

274 **Figure 2.** Laparoscopic visualization of the multiple peritoneal nodules of relapsed
275 leiomyosarcoma. Black arrows indicate the malignant lesions extended throughout the peritoneum
276 of the pelvis and abdominal wall.

277 **Figure 3.** A laparoscopic view of the large relapsed nodule of leiomyosarcoma localized in the
278 small intestine wall.

279 **Figure 4.** Triaxial PET/CT imaging of the multicentric peritoneal nodules from relapsed
280 leiomyosarcoma localized above the right common iliac artery.

281

282 **Supplemental material:** Video showing the surgical laparoscopic removal of the multicentric
283 peritoneal nodule of relapsed leiomyosarcoma localized above the right common iliac artery.

Figure 1
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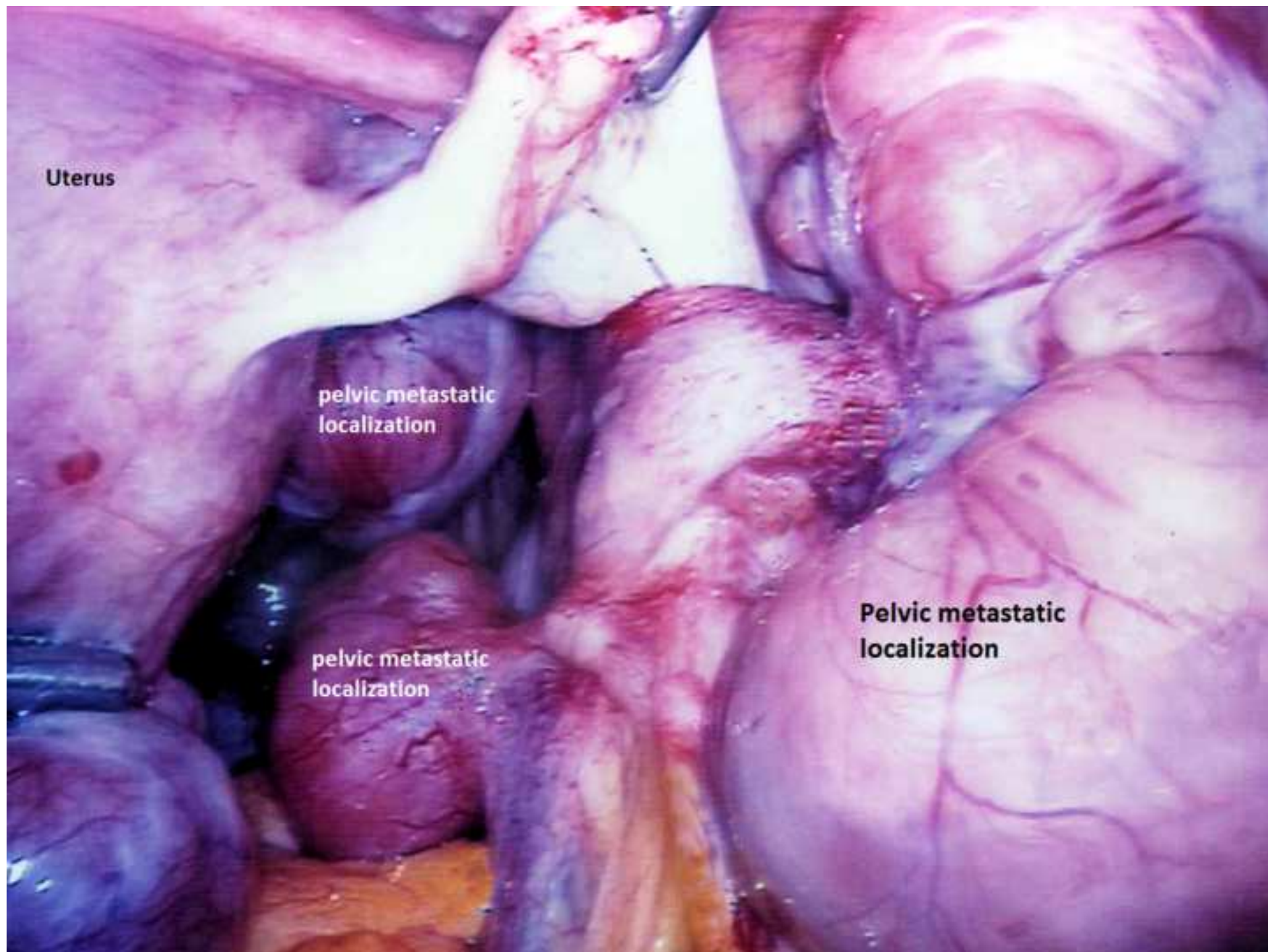


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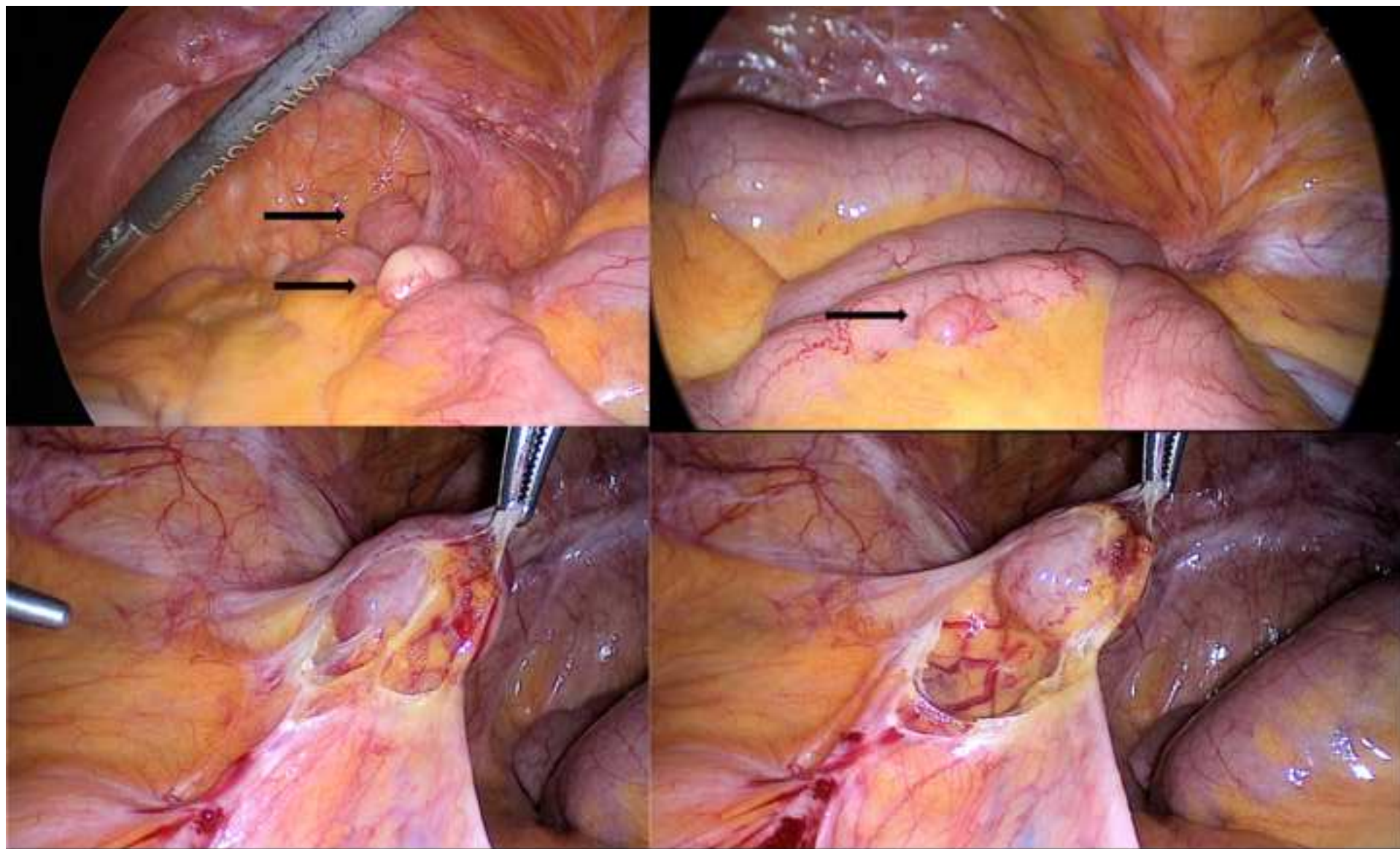


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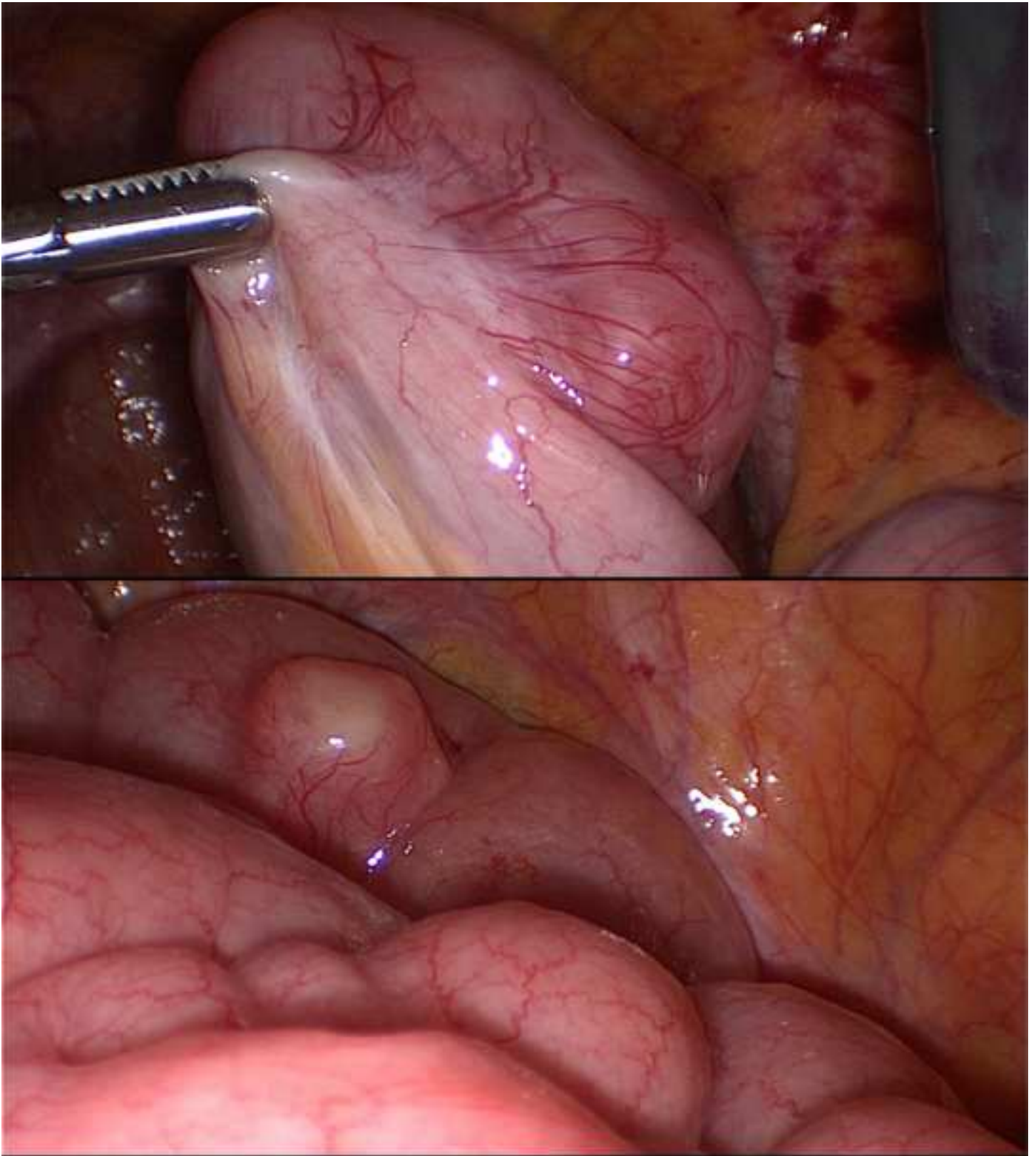
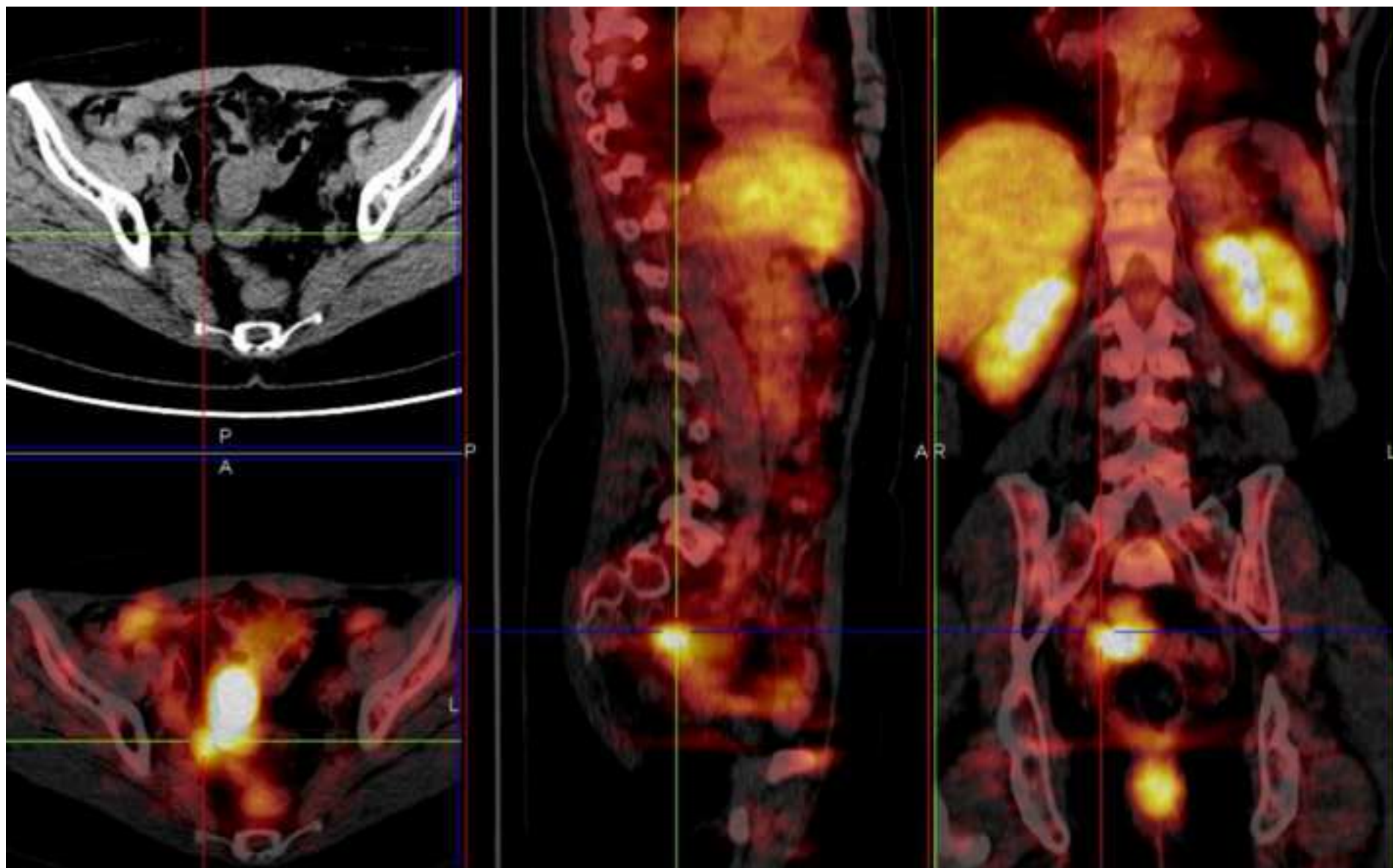


Figure 4
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Video
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