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

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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 leyomiosarcoma: 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 leyomiosarcoma. In the present paper, we describe a case of diffuse abdominal sarcomatosis from uterine leyomiosarcoma 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 leyomiosarcoma 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 leyomiosarcoma 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,
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Precìs

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.

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

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

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.

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

Introduction

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

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

Case report

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

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

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

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

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

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

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

Comment

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

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

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

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

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

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

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

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

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Figure legend

Figure 1. Laparoscpic visualization of the uterus and multiple peritoneal pelvic metastatic localizations of leyomiosarcoma at diagnosis.

Figure 2. Laparoscopic visualization of the multiple peritoneal nodules of relapsed leyomiosarcoma. Black arrows indicate the malignant lesions extended throughout the peritoneum of the pelvis and abdominal wall.

Figure 3. A laparoscopic view of the large relapsed nodule of leyomiosarcoma localized in the small intestine wall.

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

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

Figure 1

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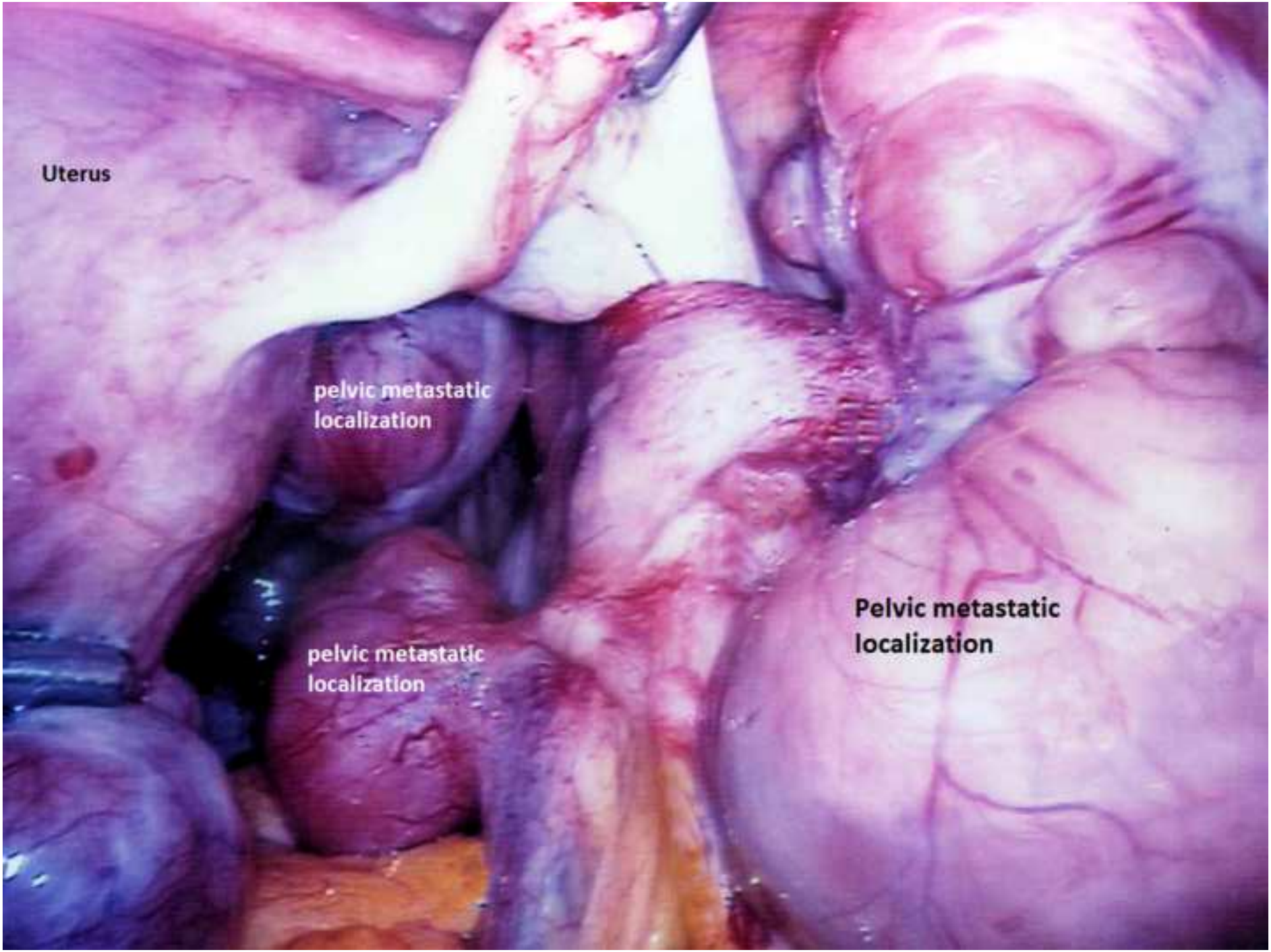

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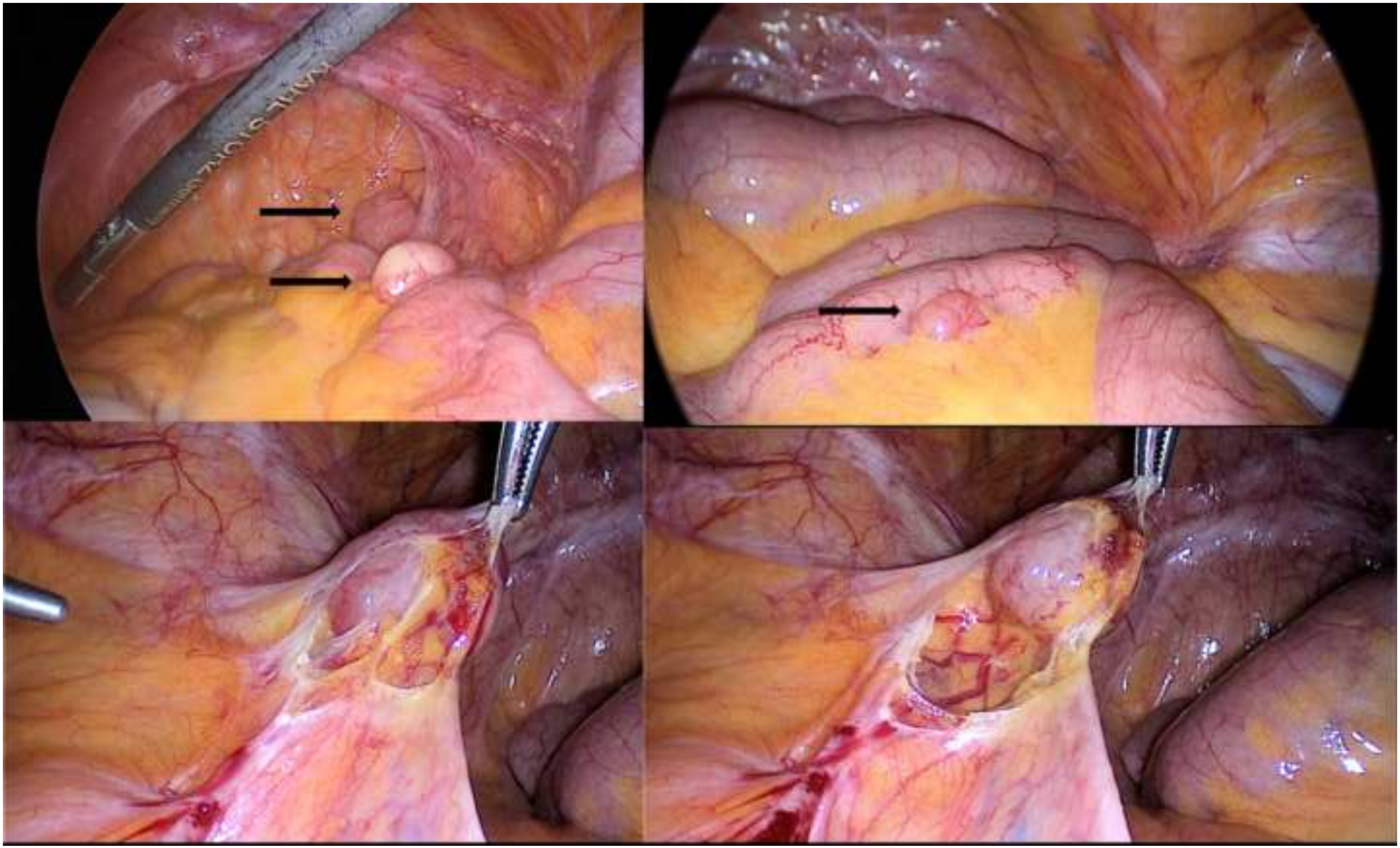

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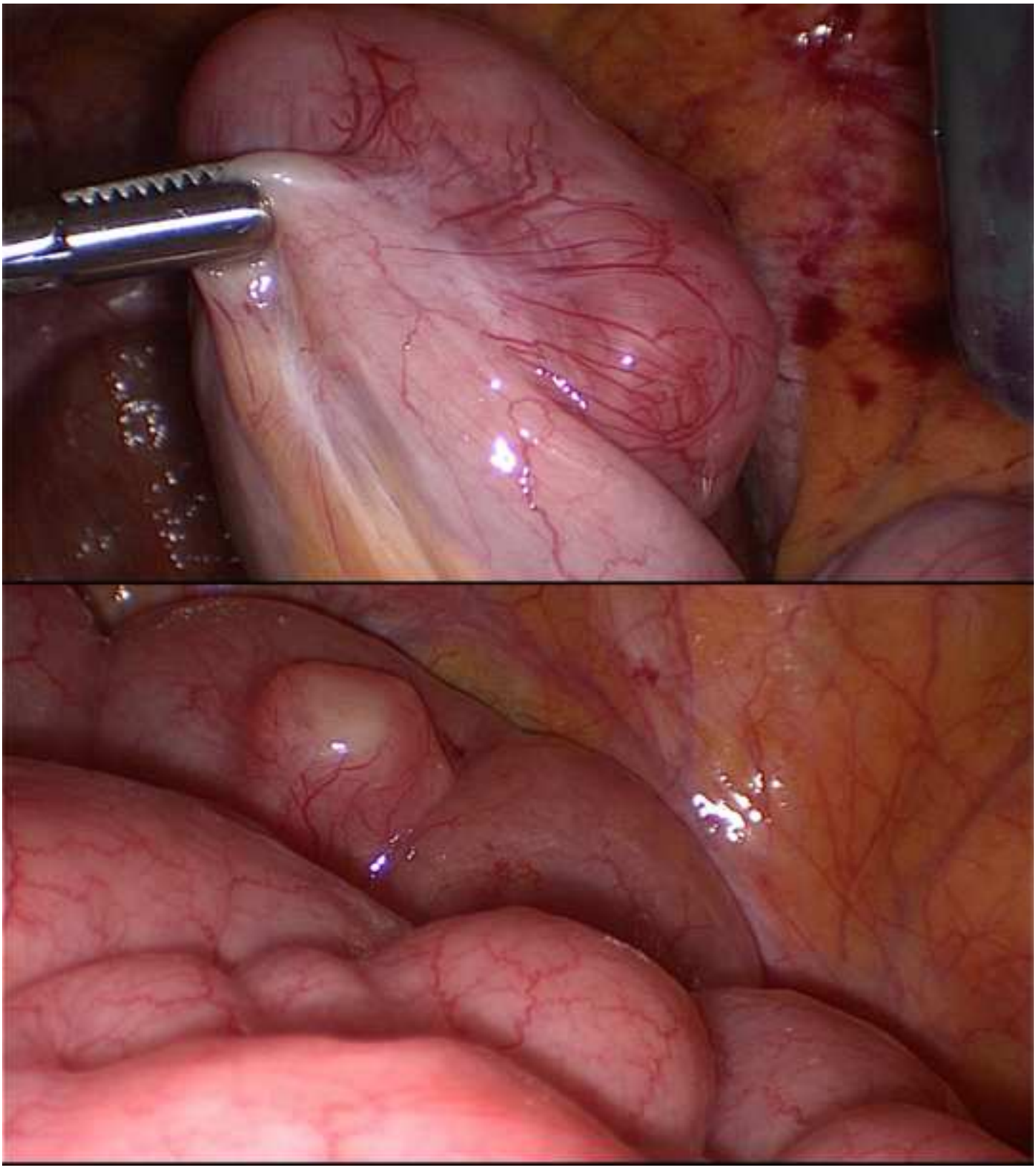

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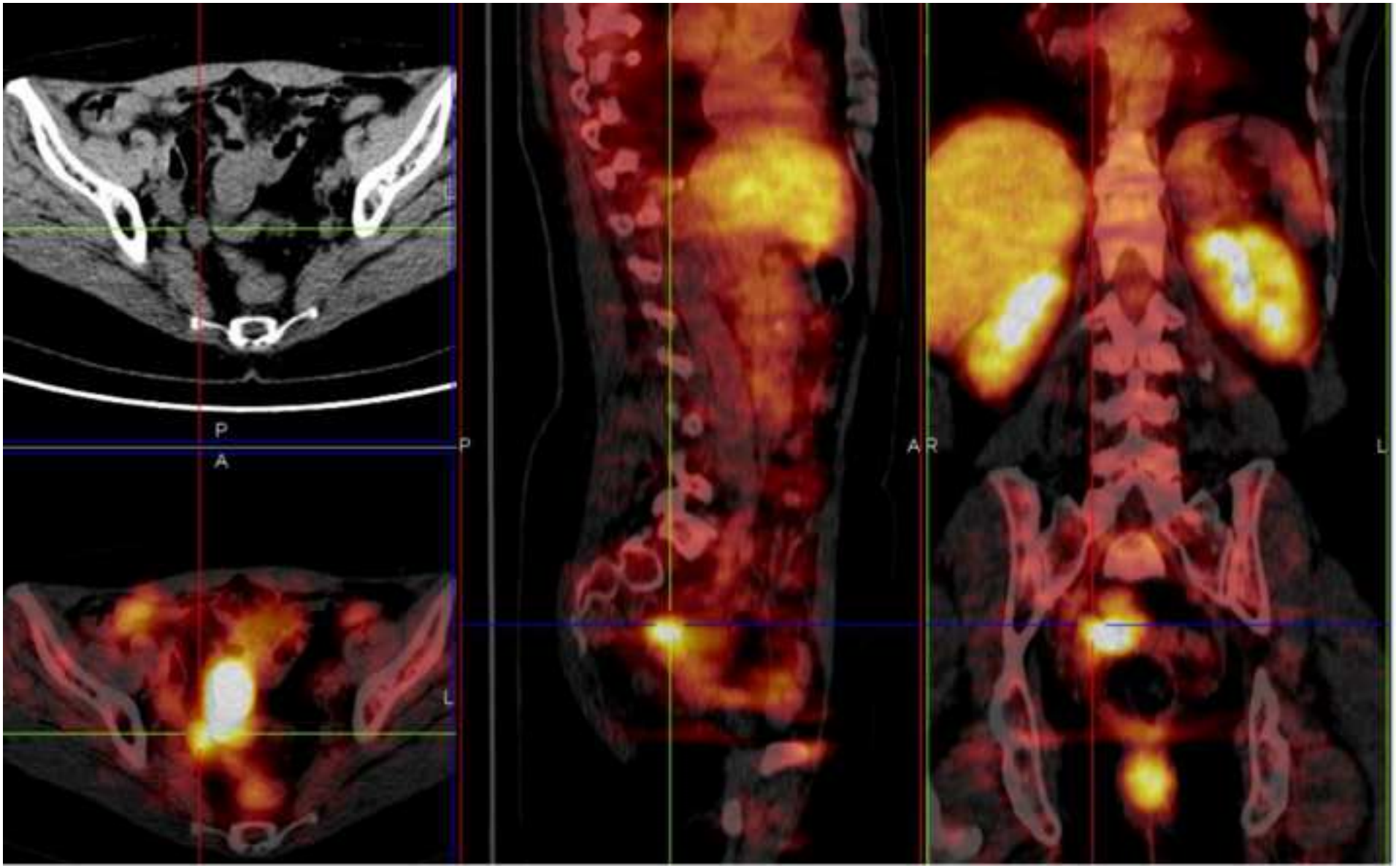

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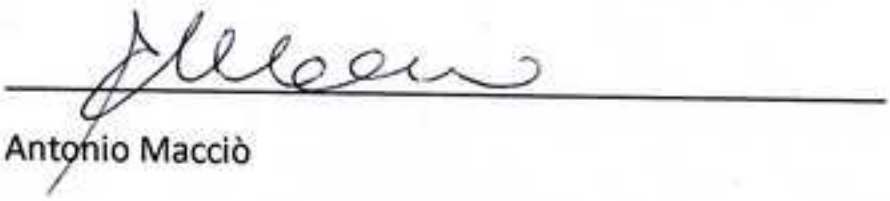

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