Metastatic renal Ewing’s sarcoma in adult woman: Case report and review of the literature

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Abstract: Primary renal extra-skeletal Ewing sarcoma is a rare neoplasm, often metastatic at diagnosis, and with a poor outcome. A multimodal approach is often the treatment of choice in this aggressive neoplasm. We present a case of primary renal extra-skeletal sarcoma in a 45-year-old woman who underwent tumor resection without clear margins. After no response to the first cycle of chemotherapy, we documented an early onset of local recurrence. The patient refused any other treatment and died four months after surgery.

Keywords: extra-skeletal Ewing sarcoma, adult Ewing sarcoma, PNET, renal tumor, surgical margins

1 Introduction

The Ewing Sarcoma (ES) family represents a group of high-grade malignancy tumors including ES of bone, Extra-skeletal Ewing sarcoma (EES), peripheral neuroectodermal tumor (PNET), and Askin tumor (a thoracopulmonary PNET). The ES family is a group of poorly differentiated tumors made up of small round blue cells and it recognizes the rearrangement of the ESWR1 gene as a pathognomonic sign [1]. The ES breakpoint region (ESWR1) maps on 22q12 and is one of the most involved genes in sarcoma, firstly identified in the ES family, but also present in other neoplasms.

ES is the second most common pediatric bone tumor, with a peak of incidence between the first and second decade and 80% of cases arise from the skeleton [2]. In adults, the most frequent primary presentation is an EES [3], which accounts for about 5% of all soft tissue sarcomas [1]. EES has no pathognomonic symptoms or signs and the clinical features depend mainly on the primary site. Potentially, EES could affect everywhere as single or multiple lesions [4]. The most common primary sites include the paravertebral spaces, lower extremities, head, neck, and pelvis. Sites rarely involved are the retroperitoneum, omentum, orbit, skin, and chest wall. The imaging features of EES are non-pathognomonic as well as clinical manifestations. It often presents as a well-defined, heterogeneous mass with areas of hemorrhage or necrosis in absence of calcification and nodal metastases [3]. EES can rarely arise in the kidney [4], resembling a renal cancer often with involvement of renal vein, inferior vena cava, or adjacent organs [3]. Most common metastatic sites in EES are lung, bone, and brain [3]. Therapeutic strategy of EES is debated. About 40–50% of the patients already present metastasis at diagnosis, so the role of the different therapies is yet to be defined. Multimodal treatment (surgery, radiotherapy, chemotherapy) determines an improvement in prognosis for single primary lesion [2], beside a poor prognosis for metastatic disease.

Herein, we report a case of an adult woman affected by an EES treated with surgery and chemotherapy. Secondary aim was to perform a review of the literature about EES and its therapeutic management.

2 Material and methods – case report

A 45-year-old female with persistent chest pain underwent chest-abdomen CT scan for suspicion of pulmonary thromboembolism. The imaging revealed a heterogeneous
A retroperitoneal mass, sized as 17 cm in diameter, extending from the superior left renal pole and infiltrating posterior abdominal wall and partially the diaphragm (Figure 1). The tumor was associated with neoplastic thrombosis of the renal vein and liver metastasis; moreover, bulky mass caused compression of the other abdominal organs and displaced them from the physiological position. The pulmonary thromboembolism was excluded, although mild left basal pleural effusion with dysventilation of the left lower lobe was evident and related to bulky mass effect. The patient was on follow-up for breast cancer treated 3 years before by surgery followed by four cycles of epirubicin and cyclophosphamide-based adjuvant chemotherapy, paclitaxel for 12 weeks, radiotherapy, and tamoxifen-based hormonal therapy, with a residual ejection fraction of 35% probably as a consequence of anthracycline therapy. Previously, she underwent also total thyroidectomy for multinodular goiter. The selective arteriography, performed 24 h before surgery, showed a mass blood supply from the first three lumbar arteries and splenic artery short branches that were embolized by hemostatic agents. A cava filter was also placed. A total body bone scan was performed for staging and was negative for bone metastasis (Figure 2).

The patient underwent a laparotomic left radical nephrectomy with adrenalectomy and partial resection of psoas muscle and diaphragm, which were macroscopically involved by tumor, in order to achieve a radical surgery. Hilar and para-aortic lymphadenectomy were also carried out. Operative time was 200 min. Estimated blood loss was 550 cc. There were not any perioperative complications. No blood transfusion was needed. The patient was dismissed on post-operatory day 13.

Macroscopic examination showed a 200 × 150 × 90 mm grey-yellow, friable mass with capsular interruption and containing necrotic and hemorrhagic areas. Surgical margins were unclear at level of psoas and diaphragm resection. Histologically, the tumor was made up of nodules separated by scler-hyaline septa and it was composed of small to medium-sized cells with oval nuclei, small nucleoli, granular chromatin, and scanty cytoplasm. The mitotic activity was high. On immunohistochemistry, the neoplastic cell resulted to be diffusely positive for CD99, focally positive for CD56, and focally and weakly positive for synaptophysin. The neoplastic cells were negative for cytokeratin (CKAE1/AE3), epithelial membrane antigen (EMA), S-100, leukocyte common antigen (LCA), CD2, CD20, CD79 alpha, CD117, LAT, CD10, MPO, TdT, CD68PGM1, NPM1, CD38, PAX5, CD31, CD34, and desmin. The proliferative index (KI67/MIB-1) was about 70%. The genetic analysis revealed the presence of EWSR1 rearrangement. The immuno-morphological analysis highlighted a malignant aggressive neoplasm with EWSR1 rearrangement, in keeping with EES. Lymph nodes were free of tumor. Four weeks after surgery, the patient underwent ESFT 2001 chemotherapy protocol, including 5 cycles of injectable vincristine (1.6 mg), ifosfamide (2.2 g), mesna (440 mg), and etoposide (110 mg). The protocol, the most suitable in this case, comprehensive of adriamycin in addition to vincristine et ifosfamide, was not administered due to the poor heart ejection fraction.

![Figure 1](image1.png) **Figure 1:** CT-scan, the imaging revealed a heterogeneous retroperitoneal mass of 17 cm in diameter containing necrotic and hemorrhagic areas, at the level of the superior left renal pole infiltrating partially the diaphragm (arrows).

![Figure 2](image2.png) **Figure 2:** Total body bone scan performed for staging revealed no bone metastasis.
After the first cycle of chemotherapy, the patient required emergency care for dyspnea. An X-ray exam showed left pleural effusion and a chest drainage was placed. A CT scan disclosed a huge recurrence in the surgical site and a peritoneal carcinomatosis as shown in Figures 3 and 4. Patient refused a second cycle of chemotherapy and died four months after surgery.

Informed consent: Written informed consent was obtained from the patient for publication of relevant medical information and all of accompanying images within the manuscript.

3 Discussion

ES was first described by Stout in 1918 and later on in 1921 by James Ewing who characterized this tumor describing it in the diaphysis of long bones. ES in children and adolescents is defined as a bone tumor, which may occur at any site within the skeleton, but preferentially affects the trunk and the diaphysis of long bones [5]. However, in 15% of cases it may occur in extra-skeletal soft tissue. On the opposite, when diagnosed in adults, ES often affects soft tissues [6,7].

About 85–90% of EES cases present a somatic reciprocal t (11; 22)(q24; q12) chromosomal translocation, which fuses EWSR1 to the FLI1 ETS family gene to generate EWSR1-FLI1 fusion transcripts which induce mitotic defects leading to genomic instability and subsequent malignant transformation [3,8,9].

A first challenge for this kind of lesion is the diagnosis. Clinical symptoms are not characteristic when present.

![Figure 3: CT-scan, the imaging revealed a huge recurrence in the surgical site (arrows) with involvement of thoracic wall.](image1)

![Figure 4: CT-scan, the imaging revealed a peritoneal carcinomatosis (arrow).](image2)

As in other pathologic conditions, radiological findings are usually not typical and present a wide spectrum of imaging features and metastatic patterns. The imaging features of primary EES on contrast-enhanced CT or magnetic resonance imaging (MRI) are bulky heterogeneous masses with frequent local invasion or with compression of adjacent organs. Retroperitoneal masses are usually large at diagnosis with 50% of lesions bigger than 20 cm [10]. Most cases show heterogeneous enhancement with large necrotic foci. Only rare cases present relatively well-defined margins, while local invasion to adjacent organs is commonly observed. The invasion of adjacent organs and nearby muscles is commonly noted in tumors of the abdomen, pelvis, and thorax as it was in our case [1,11–14].

The definitive diagnosis is histopathologic with immunohistochemical analysis. At the histological level, EES appears as poorly differentiated, small round blue cells tumor positive for the transmembrane glycoprotein CD99, vimentin, FLI1, CKAE1/AE3, and CD 117 staining and negative TLE and WT-1 [15–18] (Figure 5). The tumor cells have a pale-to-clear scanty cytoplasm and glycogen could be highlighted on PAS staining [17].

In recent literature, more and more cases of extra-skeletal sites in adults are reported. Probably, this increase is related to the availability of molecular diagnostic techniques and not to a true increase in its incidence [19].

ES of the kidney is a rare tumor in adults and it was described for the first time in 1975 by Seemayer and colleagues. Some authors suggested that the origin of ES in the kidney could be neural cells invaginated into the kidney during their development or embryonic neural crest cells migrating into the kidney and undergoing tumorigenesis [20]. The occurrence of EES in the kidney is uncommon and represents about 1% of all renal tumors.
with less than 150 cases described in literature [21,22]. Male sex is more involved with a ratio M:F of 2:1.

At diagnosis, the most common symptom is pain (in 63%), followed by hematuria in 41% and a palpable mass in 25% [22]. In our case, the patient underwent chest-abdomen CT scan for persistent chest pain and suspicion of pulmonary thromboembolism.

Regarding renal ES (Table 1), 57% of patients had metastatic disease at the time of diagnosis [23]. Almost all of the patients (89%) who underwent biopsy had a metastatic disease at time of presentation, whereas about 1/3 of the patients (35%) who did not undergo biopsy had metastatic disease at the time of diagnosis.

In our case, the huge mass showed imaging features of malignant tumor, and for this reason, we performed a surgical treatment without biopsy. Due to bulky size and wide blood supply of the tumor, a preoperative renal angi-embolization was carried out in order to reduce the risk of intraoperative bleeding and to facilitate surgical procedure, thus decreasing operative time and perioperative morbidity. Other important benefits of preoperative embolization included the potential role of an

Figure 5: Histologic findings (a–e) revealed EES appearing as a poorly differentiated, small round blue cells tumor positive for the transmembrane glycoprotein CD99, vimentin, and CD 117 staining. Hematoxylin and eosin staining (a–c) show the lesion composed by small to medium-sized cells arranged in nodules separated by sclero-hyaline septa. Synaptophysin marker (d and e).
| Reference                | Year | No of cases | Mean age (year) | Sex | Side | Symptoms at diagnosis | Mean size of tumor (cm) | Metastasis at diagnosis | Biopsy | Therapy | Median FU (months) | Outcome |
|--------------------------|------|-------------|-----------------|-----|------|-----------------------|-------------------------|-------------------------|--------|---------|-------------------|---------|
| Soni and Wei [38]        | 2017 | 1           | 28 F            |     | Left | AbP, FP                | 14                      | IVC and left renal vein | No     | RN + adjuvant chemotherapy | 36.5    | 2 CFS; 1 OS |
| Teegavarapu et al. [39]  | 2017 | 13          | 11 M; 2 F       |     | 8 left; 5 right         | FP, 2 AbP, 1 BP, 2 PM, 4 Hmt, 1 f; 1 wt loss; 1 testicular swelling | 12                      | 8 lung; 7 Rp; 1 liver; 1 LN; 1 bone; 1 brain; 1 eyes; 1 adrenal; 1 pulmonary vasculature, 11 pts with metastasis | yes    | 9 RN + adjuvant chemotherapy; 4 chemotherapy |         |         |
| Abolhasani et al. [40]   | 2016 | 1           | 21 M            |     | Right | Hmt                  | 18 × 8 × 5              | No                      | No     | No      | ND                | ND      |
| Abolhasani et al. [40]   | 2016 | 1           | 31 M            |     | Right | Hmt                  | 2 × 2 × 2               | No                      | Yes    | Neoadjuvant chemotherapy + RN | ND      | ND      |
| Abolhasani et al. [40]   | 2016 | 1           | 34 F            |     | Left  | Abd swelling, left lower chest pain, PM | ND                      | No                      | No     | No      | ND                | ND      |
| Yamamoto et al. [41]     | 2015 | 1           | 35 M            |     | Right | AbP, Hmt            | 15.5 × 13.5 × 10       | IVC, Lung               | Yes    | RN + metastasectomy          | 27      | ND      |
| Chakrabarti et al. [42]  | 2015 | 1           | 24 M            |     | Right | AbP, PM             | 6 × 5                   | No                      | No     | RN + adjuvant chemotherapy | 15      | ND      |
| Almeida et al. [43]      | 2014 | 1           | 19 M            |     | Right | FP, f; vomit        | ND                      | Lung                   | Yes    | RN + adjuvant chemotherapy | ND      | ND      |
| Liu et al. [44]          | 2014 | 1           | 37 M            |     | Left  | FP, Hmt            | 4 × 2.3 × 1.5           | No                      | No     | Open RNU + adjuvant chemotherapy | 18      | CFS     |
| Hakky et al. [20]        | 2013 | 1           | 33 M            |     | Left  | nausea, vomit, FP   | 5.1 × 4.8 × 3.3        | No                      | No     | No      | ND                | ND      |
| Richey et al. [45]       | 2012 | 1           | 50 M            |     | Right | FP, Hmt, PM        | 15.9 × 10.6             | Infracardiac and Abd LNs, renal fat and vessel, lung, liver | Yes    | chemotherapy          | ND      | ND      |
| Tariq et al. [46]        | 2012 | 1           | 57 F            |     | ND    | ND                  | ND                      | Lung                   | ND     | Multimodal                     | 96      | CFS     |
| Alonso et al. [47]       | 2011 | 1           | 20 M            |     | Left  | Hmt                  | 7                       | Lung, retroperitoneal carcinomatosis | No     | Open RN + adjuvant chemotherapy | 24      | CFS     |
| Alonso et al. [47]       | 2011 | 1           | 43 M            |     | Right | Pneumonic process   | ND                      | Lung, IVC              | No     | Open RN + thrombectomy + adjuvant chemotherapy | 9       | CFS     |
| Pathak et al. [48]       | 2011 | 1           | 44 F            |     | Right | PM                  | 17.4 × 11.5 × 9.3      | Renal vein, IVC, atrium | No     | RN + thrombectomy             | ND      | ND      |
| Mohsin et al. [49]       | 2011 | 1           | 26 M            |     | Right | FP, AbP, Hmt, wt loss, PM | 20 × 13 × 10 × 10       | Lung, lymphadenopathy, renal vein | No     | RN + adjuvant chemotherapy | 10 days | OS      |
| Mohsin et al. [49]       | 2011 | 1           | 25 M            |     | Left  | FP, Hmt, FP, PM     | 15 × 11 × 8            | Renal vein, lung, liver | No     | RN                  | 2       | OS      |
| Reference            | Year | No of cases | Mean age (year) | Sex | Side | Symptoms at diagnosis | Mean size of tumor (cm) | Metastasis at diagnosis | Biopsy | Therapy                                      | Median FU (months) | Outcome |
|----------------------|------|-------------|-----------------|-----|------|------------------------|------------------------|-------------------------|--------|---------------------------------------------|-------------------|---------|
| Mohsin et al. [49]   | 2011 | 1           | 30 F            | Right | Abd swelling, PM          | 18 × 12                | Vertebral bodies        | Yes     | Chemotherapy                               | 1                 | ND      |
| Wedde et al. [51]    | 2011 | 1           | 34 M            | Right | Hydrocele                  | ND                     | No                      | Yes     | RN + adjuvant chemotherapy                 | 7                 | CFS     |
| Badar et al. [50]    | 2010 | 1           | 13 F            | Right | AbP, Hmt                   | 6 × 9                  | Lung, liver             | Yes     | RN + adjuvant chemotherapy + RT            | 26                | OS      |
| Asiri and Al-Sayyad  | 2010 | 1           | 11 M            | Right | FP, Hmt, PM                | 10 × 9 × 11            | No                      | No      | RN + lymph node dissection + adjuvant chemotherapy | 3                 | OS      |
| Angel et al. [53]    | 2010 | 1           | 31 M            | Left  | FP, Hmt                    | 7.9                    | No                      | No      | RN                                          | 12                | CFS     |
| Ohgaki et al. [54]   | 2010 | 1           | 21 M            | Right | AbP, hemorrhage             | ND                     | No                      | No      | RN + lymph node dissection + IVC thrombectomy | 6                 | OS      |
| Fergany et al. [55]  | 2009 | 1           | 31 M            | Right | Hmt                        | 16                     | Renal vein, IVC, lung   | No      | chemotherapy                               | 24                | CFS     |
| Businger et al. [56] | 2009 | 1           | 46 F            | Right | AbP                        | 5 × 12 × 16            | Renal vein              | No      | Open retroperitoneal omentectomy with RN + adjuvant chemotherapy | ND                | ND      |
| Ishii et al. [57]    | 2009 | 1           | 21 M            | Right | ND                         | ND                     | No                      | No      | RN                                          | 6                 | OS      |
| Zhang et al. [58]    | 2009 | 1           | 41 M            | ND    | ND                         | ND                     | No                      | No      | RN + adjuvant chemotherapy + RT            | 9                 | CFS     |
| Ong et al. [59]      | 2008 | 1           | 21 F            | Right | PM, pain, Hmt, Syncope, respiratory failure, Hmt | 12.5 × 9 × 9 × 8.7    | Renal vein, IVC, atrium, lung, Pulmonary embolus, renal vein, IVU, lymphadenopathy | No     | RN + thrombectomy | 10                | CFS     |
| Koski et al. [60]    | 2008 | 1           | 78 F            | Left  | PM, pain, Hmt, Syncope, respiratory failure, Hmt | ND                     | Renal vein, IVC, psoas, spinal canal, liver | Yes    | Neoadjuvant chemotherapy + RN + thrombectomy + RT | 2 weeks           | OS      |
| Chu et al. [61]      | 2008 | 1           | 14 F            | Left  | BP, decrease of sensation, PM | ND                     | Renal vein, IVC, spinal canal, L1, lung | Yes    | Chemotherapy                               | 4.5               | CFS     |
| Chu et al. [61]      | 2008 | 1           | 16 F            | Left  | BP, decrease of sensation, PM | ND                     | Renal vein, IVC, atrium, lung | Yes    | Neoadjuvant chemotherapy + RN + thrombectomy + RT | 24                | CFS     |
| Kang et al. [62]     | 2007 | 1           | 34 M            | Left  | Hmt, pain                  | 8.6 × 6 × 3.5 × 4     | Bone                    | Yes     | RN                                          | ND                | ND      |
| Moustafellos et al. [63] | 2007 | 1           | 32 M            | Right | AbP, FP                    | 3.5 × 4.3              | No                      | No      | RN + adjuvant chemotherapy                 | 36                | CFS     |
| Parada et al. [64]   | 2007 | 1           | 19 M            | Left  | FP, fv                     | 7.5                    | ND                      | No      | Chemotherapy                               | ND                | ND      |
| Reference                  | Year | No of cases | Mean age (year) | Sex | Side | Symptoms at diagnosis | Mean size of tumor (cm) | Metastasis at diagnosis | Biopsy | Therapy | Median FU (months) | Outcome |
|----------------------------|------|-------------|-----------------|-----|------|-----------------------|-------------------------|-------------------------|--------|---------|------------------|---------|
| Ellinger et al. [23]       | 2006 | 1           | 39              | M   | Left | Hmt, testicular pain, varicocele | 12                       | Yes                     | No      | RN + adjuvant chemotherapy | 6       | CFS     |
|                            |      |             |                 |     |      | Lung, renal vein, IVC, lymph nodes | 9 x 5 x 5                 |                         | RN + thrombectomy + splenectomy + adjuvant chemotherapy | 15      | CFS     |
| Saxena et al. [65]         | 2006 | 1           | 26              | F   | Left | Dyspnea, nausea | 18 x 14 x 13 | Lung                     | Yes     | RN + adjuvant chemotherapy | 6       | OS      |
| Maeda et al. [66]          | 2006 | 1           | 6               | F   | Right | AbP, PM | 5 x 4.5 x 4.5           | No                     | No                    | RN + lymph node dissection + adjuvant chemotherapy | 90      | CFS     |
| Erkiliç et al. [67]        | 2006 | 1           | 45              | M   | Left | FP, Hmt | ND                       | No                     | No                    | RN      | Surgery + adjuvant chemotherapy | 12      | CFS     |
| Pomara et al. [68]         | 2004 | 1           | 27              | F   | Left | FP, Hmt | 11 x 8 x 6               | Renal vein              | No                    | No      | RN + adjuvant chemotherapy + RT | 24      | CFS     |
| Sivaramakrishna et al. [69]| 2003 | 1           | 27              | M   | Left | FP, PM | 16 x 11                  | Renal vein              | No                    | RN + adjuvant chemotherapy | 9       | CFS     |
| Murphy et al. [70]         | 2003 | 1           | 26              | M   | Right | Bilateral FP | 6                        | Renal vein, IVC        | No                    | RN + thrombectomy + adjuvant chemotherapy | ND      | ND      |
| Wada et al. [71]           | 2003 | 1           | 23              | F   | Right | Fatigue, fv, FP, Hmt | 13 x 10                 | Lung, renal vein IVC   | No      | RN + thrombectomy | 12      | CFS     |
| Vicha et al. [72]          | 2002 | 1           | 9               | F   | Right | PM        | 15 x 14 x 11             | No                     | No                    | RN + adjuvant chemotherapy | 5       | OS      |
| Karnes et al. [73]         | 2000 | 1           | 28              | M   | Right | Hmt, BP | 13 x 13                  | Renal vein + IVC       | No                    | RN + adjuvant chemotherapy | 12      | CFS     |
| Kuroda et al. [74]         | 2000 | 1           | 28              | M   | Left  | AbP      | 7.4 x 5.7 x 7.6         | No                     | No                    | RN      | ND      | ND    | ND    |
| Herman et al. [75]         | 1997 | 1           | 17              | ND  | Right | Abd swelling, Hmt | ND                       | ND                     | No      | RN      | ND    | ND    |
| Fontaine et al. [76]       | 1997 | 1           | 42              | M   | ND    | ND       | ND                       | ND                     | ND                    | ND      | Surgery + RT + adjuvant chemotherapy | 60      | CFS     |
| Mor et al. [77]            | 1994 | 1           | 61              | ND  | ND    | ND       | ND                       | ND                     | No                    | Surgery + adjuvant chemotherapy + RT | 6       | OS      |

FP, flank pain; AbP, abdominal pain; BP, back pain; PM, palpable mass; Hmt, hematuria; fv, fever; RN, radical nephrectomy; PN, partial nephrectomy; RNU, radical nephroureterectomy; RT, radiotherapy; IVC, inferior vena cava; LNs, lymph nodes; Rp, retroperitoneal; Abd, abdominal; wt, weight; CSF, cancer free survival; OS, overall survival.
Table 2: Nonrenal extraosseous ES/PNET

| Reference                  | Year | No of cases | Mean age (year) | Sex | Site                                 | Symptoms at diagnosis          | Mean size of tumor (cm) | Metastasis at diagnosis | Biopsy | Therapy                                    | Median FU (months) | Outcome |
|----------------------------|------|-------------|-----------------|-----|--------------------------------------|--------------------------------|-------------------------|------------------------|---------|--------------------------------------------|----------------------|----------|
| Singla et al. [78]         | 2016 | 1           | 26              | M   | Lumbar epidural space               | BP                             | ND                      | No                     | No      | Laminectomy + adjuvant chemotherapy + RT | 12                   | CFS      |
| Lu et al. [79]             | 2015 | 1           | 40              | F   | Rp in the right hepatorenal recess  | FP                             | 10                      | ND                     | No      | Tumor resection                          | 12                   | OS       |
| Mohsin et al. [49]         | 2011 | 1           | 29              | M   | Prostate                             | Burning micturation, PM         | ND                      | Bladder, lymphadenopathy, lung, pleural Lung, ascite | Yes     | Chemotherapy                              | 4                    | ND       |
| Mohsin et al. [49]         | 2011 | 1           | 20              | F   | Right adrenal                        | FP, anorexia, wt loss, PM       | ND                      | Lung, ascite            | Yes     | Chemotherapy                              | ND                   | ND       |
| Yip et al. [80]            | 2009 | 1           | 28              | F   | Near the vaginal introitus           | FP, AbP, PM                     | 21 × 17 × 12             | ND                     | No      | RT + Neoadjuvant chemotherapy + mass excision + adjuvant chemotherapy Local 15 chemotherapy + 3 surgery 9 RT Metastatic RT + chemotherapy TURB then surgery | 16                   | OS       |
| García-Morena Nisa et al.  | 2007 | 1           | 21              | F   | Rp and retrodiaphragmatic            | FP, flanck pain; AbP, abdominal pain; BP, back pain; PM, palpable mass; Hmt, hematuria; LNs, lymph nodes; Rp, retroperitoneal; wt, weight; RT, radiotherapy; CSF, cancer free survival; OS, overall survival. | ND                      | 10.5                   | 4                      | No      | Local 15 chemotherapy + 3 surgery 9 RT Metastatic RT + chemotherapy TURB then surgery Tumor resection + RN + LNs dissection | 7 CFS; 4 OS |         |
| Ellinger et al. [23]       | 2006 | 1           | 72              | M   | Bladder                              | Hmt, oliguria                   | ND                      | Prostate, Abd wall, peritoneum | No      | TURB then surgery Tumor resection + RN + LNs dissection | 2                    | OS       |
| Thebert et al. [83]        | 1993 | 1           | 22              | F   | Rp                                   | BP, AbP, PM                     | 18 × 15 × 22             | ND                     | No      | TURB then surgery Tumor resection + RN + LNs dissection | ND                   | ND       |
early ligation of the renal vein before the renal artery has been fully controlled, according to the indications given by Robson. In literature, the real usefulness of preoperative renal embolization is still debated. However, a recent prospective, randomized study showed preoperative renal embolization to be a safe and well-tolerated procedure that allowed to reduce median blood loss in patients with huge kidney cancer who underwent embolization before nephrectomy compared to patients who did not undergo preoperative embolization [24].

Prognosis is poor in metastatic disease [25–29], whereas in cases of nonmetastatic lesions a survival benefit is reported from 18 to 51 months which is best related with negative surgical margins [30–33]. Also, age (≥40 years) and dimensions of tumor (larger diameter of at least 8 cm) are considered prognostic factors associated with poor cancer-specific survival rate [34]. Our case seemed to be one of them with poor prognosis related to its huge local extension in addition to metastasis.

Multimodal approach including surgery associated to the adjuvant chemotherapy is the standard therapeutic approach, with radiotherapy (RT) playing an optional role in localized and nonsurgical tumors. However, 32.5% of patients received only surgical treatment, while 13% received only chemotherapy. In the 87% of the patients who received surgical treatment, a nephrectomy was performed. About 5.5% of surgical patients received neoadjuvant chemotherapy, 47% adjuvant chemotherapy, and 15% adjuvant chemotherapy and radiotherapy. The mean overall survival (OS) in the group of patients treated by multimodal approach was 20.8 months, whereas that in the patients who received only surgery was 10.3 months [25–32].

The key point in the management of these tumors is to obtain a complete surgical debridement with clear negative margins, but this is affected by the disease stage at diagnosis [35,36]. In our case, the multimodal approach did not improve patient prognosis with a rapid onset of local recurrence and cancer-specific survival was 4 months. This may be due to unclear surgical margins at level of psoas and diaphragm. A reasonable therapeutic approach in case of doubt to obtain clear surgical margins could be the choice of neoadjuvant chemotherapy. An eventual response to it could be the permission to perform a surgical operation. However, early relapse, within 2 years of first diagnosis, is reported in 70% of cases. In 66% of relapsing disease, it occurs at distant sites in metastatic disease at diagnosis, while isolated local recurrence is described in 20% of cases and is more frequent in ES localized at diagnosis [37].

Table 2 shows the review of the literature concerning nonrenal extraosseous ES/PNET. In this type of tumor, 26% of patients had metastatic disease at the time of diagnosis. The ratio M:F is lower than that in renal ES and it is around 1.25:1. Thirty percent of the patients underwent surgery, 50% of whom received neoadjuvant chemotherapy, 25% adjuvant one. Radiotherapy was carried out in 56% of all patients. Differences between these two groups concern metastatic disease which is more common in the renal ES one at diagnosis. In this group, the percentage of patient treated by nephrectomy was significantly higher, while neoadjuvant chemotherapy associated with radiotherapy was used in a multimodal treatment in a low percentage of cases. On the other hand, patients with nonrenal extraosseous ES received often a multimodal treatment with neoadjuvant chemotherapy associated with radiotherapy. In this group, surgical approach is not the main treatment of choice.

4 Conclusion

Reporting this case, we would point out that in presence of a renal mass, especially if huge, it has to be borne in mind that EES can occur primarily in the kidney. The local invasion should be well-evaluated before the surgery because, in case of EES, only a complete surgical ablation of the tumor could improve cancer-specific survival.

In adult, advanced ES is a dramatic condition with inauspicious outcome. Often, successful rate of surgical treatment may be affected by complexity to obtain negative surgical margins due to disease extension. Due to this, surgery in advanced disease may be considered as an important step of multimodal treatment.

Acknowledgments: We are thankful to the patient for her cooperation and allowing us to use her medical records in our case report.

Funding: This study was not supported by any external sources of funding.

Author contributions: J. A. R. V. and A. P. independently performed online bibliographic searches in order to identify titles and abstracts of interest and G. C. select full-text to be included. E. M. was responsible for conception and design. J. A. R. V., A. P. and S. F. acquired the clinical data. M. Z., S. A., G. C., S. F. and J. A. R. V. took part in either drafting the article and revising it critically for important intellectual content. All authors gave final approval of the version to be published, agree to be
accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors have read and approved the final manuscript.

Conflict of interest: Giovanni Cochetti, and Ettore Mearini serve as Section Editors in Open Medicine, but it hasnt affected the peer-review process, authors do not state any other conflict of interest.

Availability of data and materials: Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study. The authors presented, in the manuscript, all the necessary information about their case report.

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