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Recurrent Leiomyosarcoma of the Small Bowel: A Case Series

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Abstract. *Background/Aim: Leiomyosarcoma is an extremely rare, small bowel neoplasm (2% of all gastrointestinal tumours). Early diagnosis is challenging due to the slow growth of the cancer. The biological behaviour of this group of tumours is aggressive, and the first-line treatment is surgical resection. Patients and Methods: This is a report of 4 cases of small bowel leiomyosarcoma that were treated in the last ten years at Hospital San Martino: one involving the jejunum and three involving the ileum (age range=69-86 years). Three patients underwent surgical resection and one was treated with chemotherapy. Results: All patients who were eligible for surgery underwent radical resection with R0 margins. Mean overall survival was 33 months (range=8-84 months). Conclusion: Specific guidelines for small bowel leiomyosarcoma do not currently exist and these rare cases should be discussed in a multidisciplinary context. The first treatment approach is surgery, and in some cases, multivisceral resection may be needed to obtain free margins, even in recurrent cases.*

Small bowel neoplasms are very rare and represent less than 2% of all primary gastrointestinal tumours (1). In 2016, approximately 10,000 new cases of small bowel malignancies were reported in the USA and mortality was 10% (2).

These diseases are sporadic or are associated with a genetic syndrome (Peutz-Jeghers syndrome, NF1), Meckel's diverticulum, or other neoplasms (retroperitoneal sarcoma, lung carcinoid) (3).

Therapy with long-term nonsteroidal anti-inflammatory drugs (NSAIDs) may play a role in the development of small bowel alterations (4). Malignant tumours of the small bowel include adenocarcinoma, carcinoid, lymphoma, leiomyosarcoma, and GIST (5).

Leiomyosarcoma develops from smooth muscle cells and is most often observed in the jejunum, ileum and duodenum (6).

Its peak incidence is observed in males in their 60s. Patients affected by small bowel leiomyosarcoma are usually admitted to the emergency department due to abdominal pain, bowel obstruction or occult gastrointestinal bleeding (7, 8).

Symptoms are nonspecific due to the slow growth of the cancer, therefore, diagnosis is delayed and patients are treated when the disease is advanced and their general conditions are compromised (9).

Prognosis is poor and local recurrence is frequent, thus, surgery plays an important role in treatment. Radical *en-bloc* excision should be performed. Treatment planning and multidisciplinary discussion is mandatory (7, 10).

In this article, we report a case series regarding patients that were treated at Hospital San Martino for small bowel leiomyosarcoma over the last ten years.

Patients and Methods

Between 2010 and 2018, we observed four cases of small bowel leiomyosarcoma.

The histologic features were evaluated by trained pathologist in smooth muscle tumours.

Immunohistochemistry features were based detecting the following antibodies: smooth muscle actin, specific muscle actin, caldesmon, desmin, CD117, CD34 and S100 proteins.

All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and its later amendments. Informed consent was obtained from all patients included in the study.

Case 1. In March 2016, an 83-year old woman was admitted for bowel obstruction and chronic abdominal pain. Physical examination showed abdominal distension with no peritoneal reaction. A computed tomography (CT) scan showed jejunal invagination due to a mass measuring 5×2.8 cm cranio-caudal (CC) and 4×3.5 cm latero-lateral (LL).

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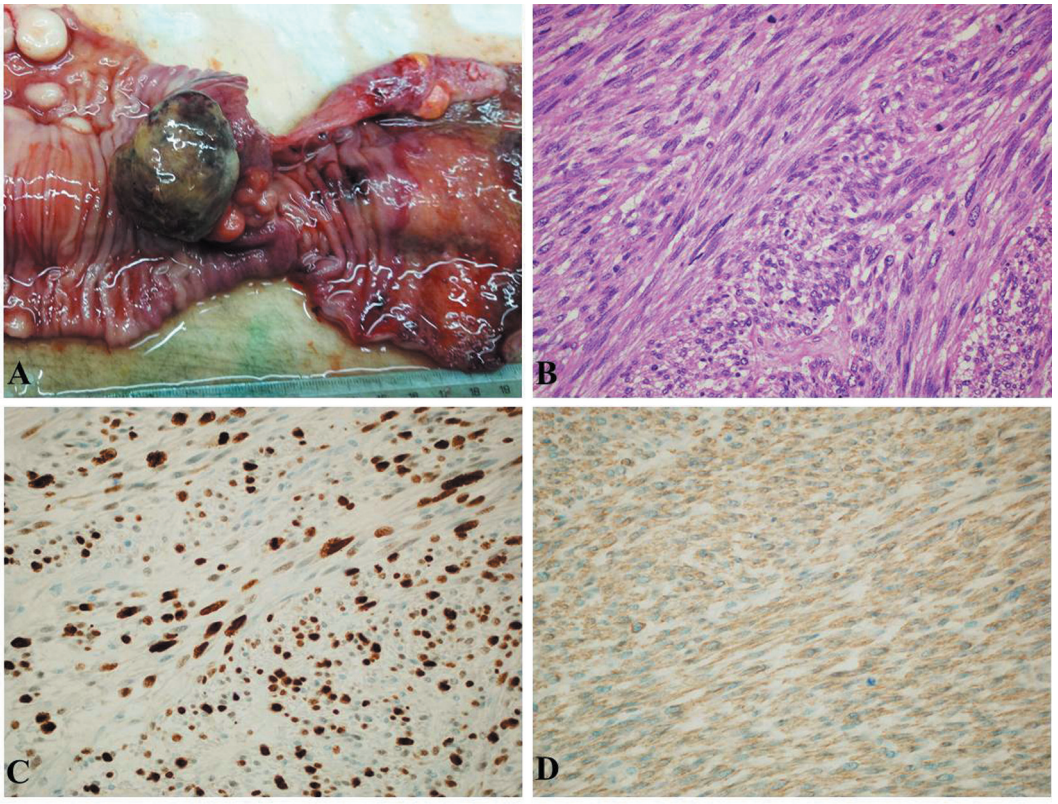

Figure 1. *Jejunal leiomyosarcoma. A) Surgical specimen showing the polypoid haemorrhagic jejunal neoplasm with small, white mucosal nodulations. B) Leiomyosarcoma characterized by a proliferation of spindle cells with atypical nuclei and numerous mitotic figure (Hematoxylin & Eosin, magnification 400×). C) Ki67 immunostaining showing high proliferation index in neoplastic cells (magnification 400×). D) Smooth muscle actin immunostaining showing diffuse positivity in neoplastic cells (magnification 400×).*

The clinical history of the patient was characterized by open cholecystectomy for cholelithiasis at a young age and arterial hypertension.

Exploratory laparoscopy of the abdominal cavity was performed that revealed adhesions between the parietal peritoneum and the omentum, and lymphadenopathy of the mesenterium. The jejunum was invaginated and presented an ulcerated neoformation 50 cm from the ligament of Treitz. During abdominal exploration, no further neoformations were detected. Lysis was carried out due to severe adherence syndrome and a wide jejunal resection was performed. The jejunum was reconstructed by a latero-lateral anastomosis.

Gross examination showed a polypoid haemorrhagic lesion (Figure 1A) near the invaginated jejunal area, which was partially circumscribed but non-encapsulated, with a maximum diameter of 8 cm. Small, white mucosal nodulations were found close to this lesion. Histology showed a leiomyosarcoma of the jejunum, with a Ki67=50% (Figure 1B and C), and negative lymph node involvement. The tumour was immunohistochemically positive for smooth muscle actin (Figure 1D), caldesmon, and desmin, while CD34, CD117 and S100 proteins were negative. Surgical margins were negative. The postoperative course was complicated by pneumonia and she was discharged on the 12th post-operative day. Following a multidisciplinary discussion with the oncologist it was decided that no adjuvant chemotherapy would be carried out on account of the general condition of the patient.

Fifteen months later she was admitted to the emergency department because of abdominal pain, bowel obstruction and a palpable mass in the left iliac fossa. CT scan showed a voluminous mass (max diameter 23 cm) infiltrating the transverse colon and ileum with concomitant carcinosis. She was treated with palliative care and died after a few days.

Case 2. In February 2017, an 86-year old man presented with abdominal discomfort and subobstruction. After ultrasound examination, CT scan showed a solid neoformation 12×9×11 cm originating from the ileum with infiltration of the mesenteric root and multiple metastatic lung nodules. Following a multidisciplinary discussion with the oncologist and the radiologist, it was decided that no surgery would be carried out on account of the locally advanced neoplasm. Percutaneous biopsy was performed.

Histological examination reported a high grade leiomyosarcoma with pleomorphic cells of the ileum. The tumour was immunohistochemically positive for smooth muscle actin, caldesmon, and desmin, while CD34, CD117 and S100 proteins were negative. Tebectedine-based therapy was started but the patient died 11 months after diagnosis due to a massive ischaemic stroke.

Case 3. In May 2012, a 79-year old woman underwent ileal resection because of an obstructive mass. Histological examination showed a low grade leiomyosarcoma of the ileum with negative

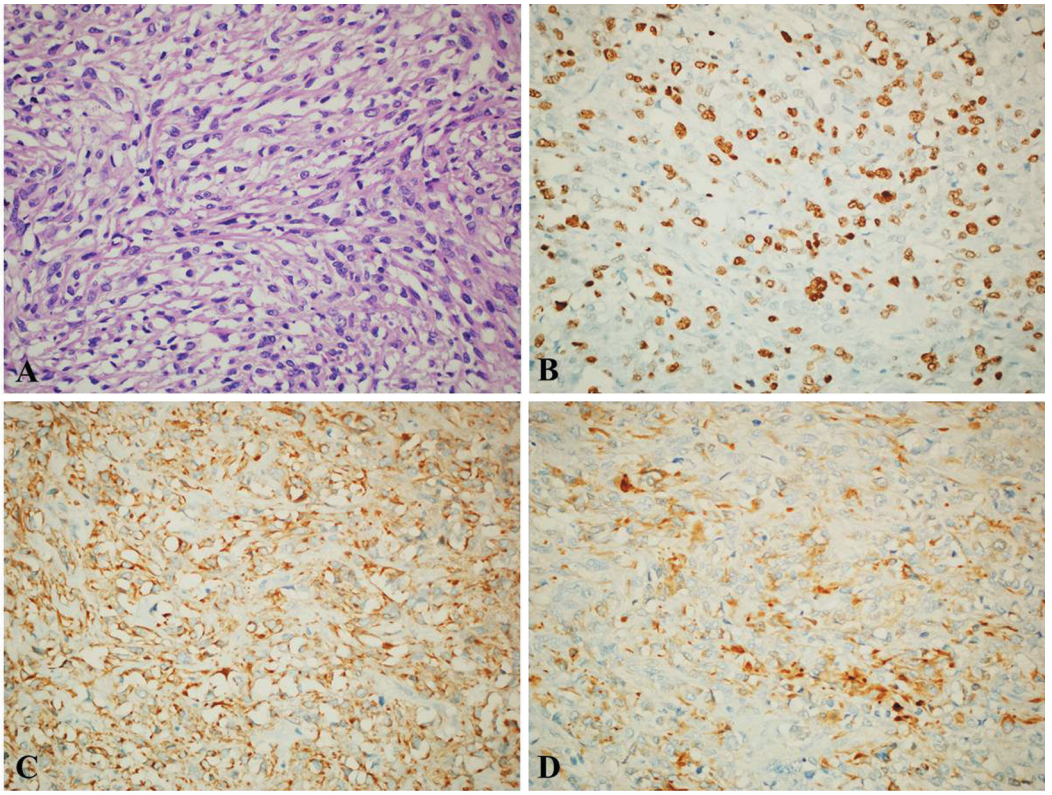

Figure 2. *Recurrent high grade leiomyosarcoma. A) Neoplastic proliferation characterized by atypical spindle-shape cells (Hematoxylin & Eosin, magnification 400×). B) Ki67 immunostain showing high proliferation index in neoplastic cells (magnification 400×). C) Smooth muscle actin immunostaining showing diffuse positivity in neoplastic cells (magnification 400×). D) Desmin immunostaining showing diffuse positivity in neoplastic cells (magnification 400×).*

surgical margins and negative nodes. In September 2017, CT scan showed a recurrent leiomyosarcoma involving the ileum, descending colon and rectus abdominis muscle. Exploratory laparotomy of the abdominal cavity was performed and revealed first severe adherence syndrome. The tumour mass had infiltrated two ileum loops and spread to the descending colon and left rectus muscle. The disease was locally advanced without peritoneal carcinomatosis. After lysis of the adhesions we performed *en-bloc* resection of a part of the left rectus muscle, descending colon, sigma and ileum. The ileum was reconstructed by two latero-lateral anastomoses, and the descending colon was reconstructed by a terminal-terminal anastomosis. Protective ileostomy was carried out. Gross examination showed a mass between the descending colon and the ileum with a maximum diameter of 15 cm. Histology revealed a recurrent high grade leiomyosarcoma with Ki67=35% (Figure 2A and B), negative nodes and negative surgical margins. Neoplastic elements infiltrated the full-thickness of the ileus, while the descending colon was infiltrated to the submucosal layer. The tumour was immunohistochemically positive for smooth muscle actin (Figure 2C), caldesmon, and desmin (Figure 2D), while CD34, CD117 and S100 proteins were negative. Surgical margins were negative. The postoperative course was complicated by an abdominal abscess treated with medical therapy. No adjuvant therapy was scheduled by the oncologist and the patient is alive with no evidence of recurrence.

Case 4. In September 2016, a 69-year old man was admitted to another Hospital where he underwent ileum resection because of acute peritonitis caused by perforation of the small bowel. The final histological report indicated leiomyosarcoma of the ileum. Margins were not described in the pathological report. No adjuvant therapy was prescribed.

In April 2017, he was admitted to our unit due to chronic abdominal pain, intermittent bowel obstruction and a palpable mass in the right iliac fossa.

The patient's clinical history was characterized by type II diabetes mellitus, chronic kidney disease, and anterior resection of the rectum due to adenocarcinoma thirty years earlier.

A CT scan was carried out and post contrast images showed a lesion involving the ileum and infiltrating the caecum, measuring 10×8 cm (CC) and 5×4 cm (LL).

A multidisciplinary discussion was set up with the radiologist and the clinical oncologist.

The patient underwent elective laparotomy, which showed that the tumour mass had infiltrated the ileum and spread to the caecum and abdominal wall. The disease was locally advanced without peritoneal carcinomatosis. We therefore proceeded to the *en-bloc* resection of the ascending colon and part of the transverse colon extending to the parietal peritoneum and ileus. We reconstructed the bowel transit with a primary ileocolonic anastomosis. Gross examination showed a firm nodular haemorrhagic lesion, partially

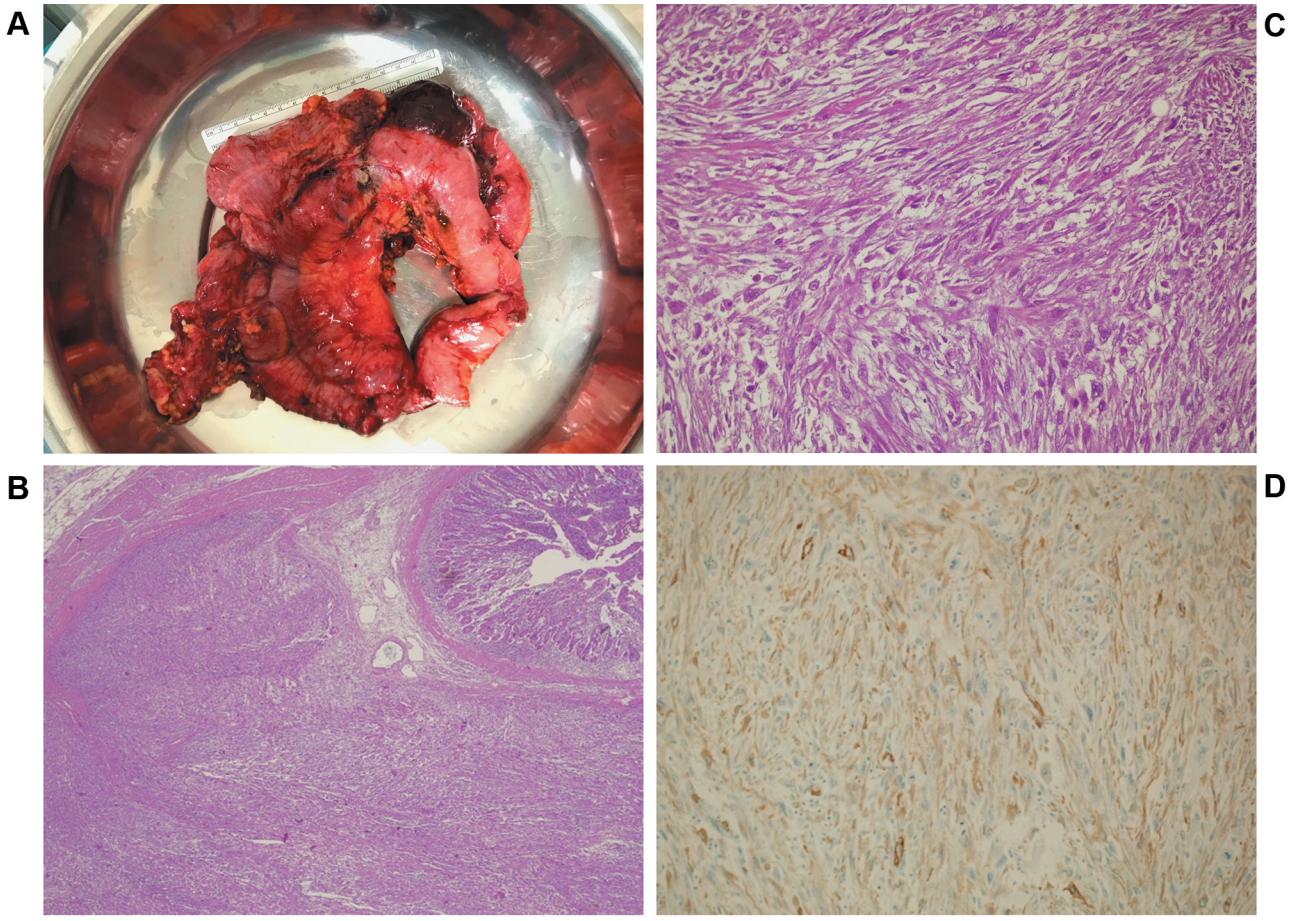

Figure 3. *Recurrent high grade leiomyosarcoma. A) surgical specimen showing polypoid haemorrhagic ileal neoplasm with firm nodulations. B) Neoplastic proliferation characterized by atypical spindle-shape cells (Hematoxylin & Eosin, magnification 2×). C) Neoplastic proliferation characterized by atypical spindle-shape cells (Hematoxylin & Eosin, magnification 20×). D) Smooth muscle actin immunostaining showing diffuse positivity in neoplastic cells (magnification 400×).*

circumscribed but non-encapsulated, with a maximum diameter of 14 cm (Figure 3A).

Histology showed that the neoplasm was composed of spindle cells, organized in a storiform pattern with a variable grade of atypia (Figure 3B and C).

Neoplastic elements infiltrated the full-thickness of the ileum, while the caecum was infiltrated to the submucosal layer.

The tumour was immunohistochemically positive for smooth muscle actin (Figure 3D) and caldesmon, while desmin, CD34, CD117 and S100 proteins were negative. Surgical margins were negative.

The postoperative course was not complicated; however, the patient was discharged on the 24th postoperative day for social reasons.

Twelve months after surgery the patient was in good conditions and neither a CT scan or PET showed any recurrence.

Results

Between 2010 and 2018, we treated four cases of small bowel leiomyosarcoma at our Hospital: one involving the jejunum and three involving the ileum.

All patients had nonspecific symptoms; bowel obstruction was the most common one, and CT scan imaging often revealed abdominal masses, which had in some cases infiltrated adjacent organs.

All patients who were eligible for surgery underwent radical resection with RO margins. Mean overall survival is currently 33 months (range=8-84 months). Our complete case series is reported in Table I.

Discussion

Leiomyosarcoma of the small bowel is a rare entity that typically becomes symptomatic when the tumour is highly infiltrating and spreads along the abdominal viscera (11). Early diagnosis is challenging mostly due to the absence of specific symptoms: they are usually diagnosed as bowel obstruction or bleeding, with non-specific abdominal pain or discomfort (7, 8, 10).

Table I. *Our case series of small bowel leiomyosarcoma from 2010 to 2018.*

	Age	Gender	Site	Status	OS (month)	Outcome
Patient 1	83	F	Jejunum	Pos (LR)	15	Dead
Patient 2	86	M	Ileum	Pos (DR)	12	Dead
Patient 3	78	F	Ileum	NED	84	Alive
Patient 4	69	M	Ileum	NED	21	Alive

Pos: Positive; NED: not evidenced disease; LR: local recurrence; DR: distant recurrence; OS: overall survival.

Table II. *Reports in the literature confirming our surgical policy for small bowel leiomyosarcoma.*

Year	Author	Site	Symptoms	Recurrence	DFS	MALIG ASS
1998	Eriguchi *et al*.	Jejunum	Pain	Yes	11	No
2000	Takemoto *et al*.	Ileum	Pain	Yes	14	Yes
2003	Acar *et al*.	Ileum	Pain	Unknown	Unknown	No
2005	Noureldine *et al*.	Jejunum	Pain	No	14	No
2012	Arts *et al*.	Jejunum	Bleeding	No	Unknown	No
2015	Ullah *et al*.	Jejunum	None	Unknown	Unknown	Yes
2015	Luis *et al*.	Ileum	Bleeding, Pain	Unknown	Unknown	No
2016	Guzel *et al*.	Ileum	Pain	No	12	No

Malig Ass: Malignant association; DFS: disease-free survival.

Megibow *et al*. (12) consider CT scans helpful for evaluating these tumours and diagnosing lesions stemming from the bowel. However, leiomyosarcomas do not have a particular pattern but may be exophytic, lobulated or irregular-shaped, and thus the usefulness of the CT scan is limited in establishing the location of the tumour.

Fidler *et al*. (13) describe MR imaging and entero-MRI of the small bowel as the most complete examination, because it provides greater tissue contrast than CT scans and better definition of the small bowel wall.

Although these techniques are extremely useful for chronic conditions like Crohn's disease, they are not indicated in an emergency context.

Surgical approach is the only curative treatment for this kind of lesion (7-9) and the prognosis is determined by tumour size and histological grading (11). The aim of surgery is to fully resect all macroscopically visible tumour tissue and to obtain histologically free surgical margins. In order to obtain a radical *en-bloc* resection, multivisceral surgery should be considered as the first approach.

The histological diagnosis of leiomyosarcoma is based on its similarity to sarcoma, which is immunohistochemically positive for SMA, desmin, and caldesmon, and negative for *CD117, CD34, DOG1, C-KIT* and *PDGFRA* mutation. Differential diagnosis with gastrointestinal stromal tumours (GIST) is represented by lack of CKIT expression (14).

Despite achieving loco-regional control through surgery, patients affected by small bowel leiomyosarcoma have poor prognosis because the risk of recurrence is high.

The role of chemotherapy is still controversial for this group of neoplasms (6) and adjuvant chemotherapy is rarely indicated.

Moreover, the surgical treatment of recurrent disease is still debated.

We usually perform extended surgery with radical intent rather than a segmental resection in order to prevent local recurrence, which may occur in these specific cases due to the aggressive features and biology of the disease. The same strategy is adopted even in the presence of recurrent disease.

Few reports confirming our surgical policy for small bowel leiomyosarcoma can be found in the literature (Table II).

Only a small number of publications have suggested a genetic predisposition on the association between other tumours and small bowel leiomyosarcoma: Dal Cin (15) *et al*. performed chromosomal analysis of tumour cells on a 4-day old culture from a collagenase disaggregated specimen of the surgically excised tumour, and numerical and structural abnormalities were observed in 11 of 27 metaphases.

In case 4 we tested KIT (ex 9, 11, 13, 14, 17) and *PDGFRA* (ex 12, 14, 18) by molecular analysis, but no significant findings were found.

Conclusion

Since small bowel leiomyosarcoma is an extremely rare disease, specific guidelines do not exist. Surgeons and oncologists usually follow the same therapeutic indications as for retroperitoneal sarcoma to treat this disease. Therefore, surgical excision with negative margins (R0) is the main goal of treatment. Multivisceral resection may be needed to achieve radical treatment even in the presence of recurrent disease. Indications for systemic therapy or radiotherapy before or after surgery have not yet been defined.

Since no specific guidelines exist, multidisciplinary discussion among surgeons, oncologists, radiologists, radiotherapists and pathologists at a reference centre is advisable in order to evaluate all major prognostic factors including performance status, stage, grading, and metachronicity.

Conflicts of Interest

Cecilia Ferrari, Stefano Di Domenico, Matteo Mascherini, Matteo Santoliquido, Luca Mastracci, Franco De Cian declare that they have no conflict of interest regarding this study.

Authors' Contributions

Cecilia Ferrari: primary author (wrote most of the paper), conceived the ideas of the study, collected data; Stefano Di Domenico: review of the scientific content (Surgery) of the manuscript, collected data; Matteo Mascherini: collected data; Matteo Santoliquido: collected data; Luca Mastracci: review of the manuscript, review of the scientific content (Pathology) of the manuscript; Franco De Cian: review of the manuscript, review of the scientific content (Surgery) of the manuscript, Professor and chief of the department where the patients had their operations (Hospital San Martino, Clinica chirurgica 1) and principal surgeon.

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