Pediatr Surg Int (2007) 23:315–322
DOI 10.1007/s00383-007-1890-1

ORIGINAL ARTICLE

Mature and immature teratomas: results of the first paediatric Italian study

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Accepted: 8 January 2007 / Published online: 28 February 2007

Abstract Teratoma is the most common germ cell tumour in childhood; mature (MT) and immature teratomas (IT) are benign tumours, but if they recur, they can be in some cases malignant. The aim of this paper is to evaluate Italian patients with MT and IT enrolled from 1991 to 2001, in a prospective multicentric study. One hundred and eighty-three patients, observed in 15 Italian Centers of Paediatric Oncology and three Paediatric Surgical Units were enrolled. Clinical data, treatment and results were all analysed. Initial evaluation and subsequent follow up included clinical examination, tumour markers and imaging procedures. Surgical resection was recommended for all the tumours. Histology was centrally reviewed and IT was classified as grading 1–3. Chemotherapy (CT) with Vinblastine, D-actinomycin and cyclophosphamide was indicated for extra-testicular IT grade 2 or 3. MT

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was diagnosed in 127 patients (93 F and 34 M, age 1–192 months, median 24): 58 patients had gonadic tumour (23 testicular, 35 ovaric), 69 extragonadic (45 sacrococcygeal, 11 mediastinic, 7 retroperitoneal, 6 in other sites). A complete resection was performed in 117 patients, a partial resection in eight patients and biopsy in one. IT was diagnosed in 56 patients (34 F, 22 M, age 1–168 months, median 7). The *T* grading was 1 in 14 cases, 2 in 26, 3 in 16; 28 had gonadic *T* (17 ovary, 11 testis), 28 extragonadic (sacrococcygeal 19, mediastinic 3, retroperitoneal 2, other sites 4). CT was administered in eight patients; 15/182 patients relapsed (1 in a metastatic site) and in 5/15 the relapse showed malignant histology. Seven MT (5.5%) relapsed (five sacrococcygeal, one retroperitoneal, one mediastinic): surgery at diagnosis had been complete in five and with residual in two; the relapse was malignant in two patients with sacrococcygeal (sc) tumours, who had a complete resection and a partial resection respectively. Eight IT (14.2%) relapsed (four ovary, three sc, one retroperitoneal). The initial surgical resection had been complete in one, with residual in six, and a biopsy had been performed in one. A malignant recurrence occurred in two patients with sc tumours (after partial resection in one and after biopsy + CT in one) and in one patient with ovarian IT after a partial resection. All the patients underwent surgical excision of the recurred mass; CT according to Protocol for Malignant GCT was administered to those who had malignant recurrence; 122/126 patients with MT and 53/56 with IT are alive without disease with a follow up of 8–144 months (median 56). Two patients with malignant relapse (one with sc MT, one with sc IT) died because of the progression of the disease. Another two died due to severe malformations (one MT, one IT) and three were lost to follow up (two MT, one IT). The overall survival (OS) at 10 years is 98% (95% CI 93.9–99.4); the event free survival (EFS) is 90.4% (95 CI 84.8–94.0). At Cox analysis no significant difference in EFS was found regarding age and site of the primary tumour, while females ($P = 0.011$), patients with grade 1–3 histology ($P = 0.025$) and patients with incomplete resection appeared at higher risk of death or relapse ($P < 0.001$), with a seven, three and eightfold increase in risk, respectively. Our data showed that incomplete resection and female gender are important risk factors for relapse or death, more so than IT histology. The number of patients treated with CT is not sufficient to evaluate the efficacy of CT in avoiding malignant relapse.

Keywords Mature teratoma · Immature teratoma · Childhood tumours · Treatment and outcome

Introduction

Teratomas are the most common germ cell tumours in children. They arise from the totipotential primitive germ cell and are composed of tissues derived from two or three germ cell layers.

These neoplasms are classified in: (1) mature teratomas (MT), if they are characterized by differentiated tissues; (2) immature teratomas (IT), if composed by some immature, non malignant tissues; (3) malignant teratomas, if features of yolk sac tumor, corioncarcinoma or embryonal carcinoma are encountered among the differentiated tissues. In rare cases, other malignant tumors, such as soft tissue sarcomas or neuroblastomas, may be found in the context of these germinal tumors. If malignant elements are mixed with teratomatous tissue, the biological and clinical features are those of a malignant tumor.

Since IT contain varying amounts of neuroectodermal or blastemal tissues, they are classified according to a ''grading'', on the basis of the amount of immature tissue present. The grading system utilized was introduced by Norris et al. [1] and modified by Gonzales Crussy [2].

MT and IT usually demonstrate a benign clinical behavior, however they may recur with potentially malignant features.

A prospective multicentric study on non-malignant teratomas was activated in the context of the Italian Association of Pediatric Hematology and Oncology. The study intended to gain more knowledge on these tumors, and to investigate the prognostic factors, in terms of local relapse and outcome.

The aim of this paper is the analysis of the clinical features and the treatment results of the patients enrolled in the study.

Patients and methods

Patients

Between January 1991 and December 2001, 183 patients with newly diagnosed MT and IT were enrolled in this national study from 15 Italian Centers of Paediatric Oncology and three Paediatric Surgical Units. Eligibility criteria required histological diagnosis of mature or immature extracranial teratoma, free of malignant elements. A central histology review was performed by R.A. (Section of Pathology, Department of Oncologic Sciences, University of Padua) and a grading classification, according to the Gonzales Crussy system [2], was applied. The protocol was ap-

proved by an institutional review board. Parents and/or guardians provided written informed consent before participation. Clinical data, laboratory tests, imaging data, surgical notes, treatment and results were obtained from the clinical records.

Status and late effects were asked for in 6-monthly follow-up questionnaires.

Clinical investigations

In all the patients the initial diagnostic investigations included history, physical examination (documenting any congenital abnormalities), complete blood count, routine blood chemistry, and serum levels of tumor markers, αFP and β-HCG.

Pre-operative radiographic studies were performed according to the tumour sites and patients' age and generally included chest radiograph, sonographic ultrasound (US) and computed tomography (CT) scan of the primary tumour.

US and/or CT scan of the tumor site had to be performed at diagnosis, and after the end of treatment every 6 months for 2 years, and every year thereafter. Serum levels of αFP and β-HCG were recommended once a week, from the time of the surgical resection until their normalization, and then at the time of the US.

Histopathology

All histopathologic samples were evaluated by the local pathologist and reviewed centrally by the pathologist in charge for the national GCT Study, located at the Section of Pathology, Department of Oncologic Sciences, University of Padua.

The tumours were histologically classified according to the World Health Organization (WHO) classification [3]. The tumour grading was defined as follows [2]:

Mature teratoma

- Grade 0: all component tissues are well differentiated

Immature teratoma

- Grade 1: <10% microscopic foci contain immature tissues
- Grade 2: 10–50% of immature tissue
- Grade 3: >50% of immature tissue

Treatment guidelines

Surgery

Primary surgical resection was indicated for all patients enrolled into this study. The excision of the tumour was considered complete if the mass had been resected in toto without evidence of rupture.

If macroscopic residual had been left or rupture of the tumour had occurred during the surgical procedure, the resection was defined incomplete.

Surgical biopsy had to be performed if the excision of the mass was considered not feasible, according to the imaging, or the intra-operatory findings.

Specific guidelines were recommended for some specific sites. For the ovary the surgical approach had to be made through a transversal, subumbilical incision or a Pfannestiel incision.

The procedure included the excision of the tumour with the ovary (preserving the salpinx if possible), the inspection of the controlateral ovary, the biopsy of regional lymph-nodes (iliac), the biopsy of suspected areas and peritoneal fluid sampling for cytologic examination when it was present.

For the testis, an inguinal orchidofunicolectomy was the recommended therapy and every manoeuvre had to be performed after clumping of the spermatic cord.

A complete en-bloc resection of the coccix was mandatory for sacrococcygeal teratomas, otherwise the resection was considered incomplete.

For teratomas localized in other sites, the general guidelines had to be followed.

Chemotherapy

Adjuvant chemotherapy was recommended 1 week after the surgical procedure, only for patients with extra-testicular IT, grade 2 and 3, independently of the presence of residue after the initial surgery. The chemotherapeutic regimen provided Vinblastine (3 mg/m^2 day 1), D-actinomycin (1,5 mg/m^2 day 1), and cyclophosphamide (800 mg/m^2 day 2); two courses were given with a 3 week-interval between the first and the second one.

Statistical analysis

Descriptive statistics were computed as median and range for continuous variables, and as absolute frequencies and percent for categorical variables. Cumulative survival and event-free survival (including death and relapse) were computed by means of Kaplan-Meier method. The role of selected risk factors for EFS

was assessed by means of univariate Cox regression. No multivariate model was fitted due to insufficient power. Stata 8 (Stata Corp, College Station, TX) was used for computation. A two sided P-value <0.05 was considered statistically significant.

Results

Patients characteristics

One hundred and eighty-three patients with MT and IT were enrolled into this study. Clinical data and characteristics of the patients are listed in Table 1.

Four patients with MT and four with IT had associated congenital malformation: aganglionar megacolon one, urogenital and severe pulmonary hypoplasia one, Currarino syndrome two, severe pulmonary stenosis one, down syndrome one, tracheomalacia one, encephalic malformation one.

A diagnosis of MT was obtained in 127 patients (34 males and 93 females); one patient with teratoma of the mastoid was not valuable due to missing data regarding treatment and outcome. The age of the patients ranged from 0 to 192 months (24 months); 40 out of 126 were less than 4 months old at diagnosis.

In 58 cases the site of the primary tumour was gonadal: 35 ovarian, 23 testicular. In 68 cases the site was extragonadal: 45 sacrococcygeal (sc), 11 mediastinal (med), 7 retroperitoneal (rp), 1 neck, 1 liver, 1 eye, 1 salivary gland, 1 tongue. Serum level of αFP was evaluated in 57 patients: in 13 newborns the values ranged from 2,000 to 126,000 ng/ml (median 29,000), in 7 patients aged 1–4 months, from 71 to 15,000 (median 276); in patients aged >4 months from 1 to 44 (median 7 ng/ml).

A diagnosis of IT was obtained in 56 patients (34 females and 22 males) whose age ranged from 1 to 168 months (median 7 months); 22 out of 56 were less than 4 months at diagnosis. According to the reported classification system, 14 cases (25%) were classified as grade 1, 26 cases (46.4%) as grade 2, and 16 cases (28.5%) as grade 3.

In 28 cases the site of the primary tumour was gonadal: 17 ovarian, 11 testicular. In 28 cases the site was extragonadal: 19 sc, 3 med, 2 rp, 2 neck, 1 rino-pharinx, 1 diaphragmatic region. Serum level of αFP was referred for 38 patients: the value ranged from 1,110 to 128,000 ng/ml (median 4,400) in 8 newborns; from 23 to 1,850 (median 308) in five infants aged 1–4 months; from 0.9 to 900 (median 42) in children aged >4 months; in four patients, aged 8, 9, 13, 14 years, αFP levels were, respectively: 500, 900, 900, 113 ng/ml: all of them had ovarian teratoma grading respectively 2, 2, 2, 3.

Table 1 Characteristics of the patients

	MT	IT	Total
Sex			
F/M	92/34	34/22	126/56
Age			
Range	0–192	1–168	0–192 mo
Median	24	7	18 mo
Primary site of T			
Sacrococcix	45	19	64
Ovary	35	17	52
Testis	23	11	34
Mediastinum	11	3	14
Retroperitoneum	7	2	9
Other sites	5	4	9
Grading of T			
0	126		
1		14	
2		26	
3		16	
Surgery			
Complete	117	45	162
Partial	8	10	18
Biopsy	1	1	2
Chemotherapy [a]			
Yes	–	8	8
No	–	25	25
Relapses	7	8	15
Exitus [b]	1	3	4
Lost to follow up	2	1	3
Survivors	122	53	175

[a] Chemotherapy was indicated in 33 patients only

[b] Two exitus for malformation, two for progressive disease

MT mature teratomas, *IT* immature teratomas, *mo* months, *y* years, *T* tumour

Treatment

Surgery

Mature teratoma A macroscopically complete resection of the mass was obtained at diagnosis in 117/126 patients; an incomplete resection with evidence of residual tumour was obtained in eight (sc tumours), and a surgical biopsy was performed in one (sc tumour).

Immature teratoma A macroscopically complete resection was performed in 45/56 patients: the tumour grading was 1 in 13 patients, 2 in 23 and 3 in 9. A partial resection was obtained in ten patients (tumour grading one in one patient, two in three and three in six), and a surgical biopsy performed in one (tumour grading 3).

Chemotherapy

According to the guidelines of the protocol, chemotherapy was indicated for 33 patients with extra-gonadal

IT grade 2–3, completely or not completely resected; however in 25 of these, with a violation of the protocol, chemotherapy was not given for parents' refusal or decision of the responsible physician.

Outcome

Mature teratoma Out of 126 patients, three are not valuable: two were lost at follow-up, one died for severe encephalic malformation and disseminated intravascular coagulopathy, occurred after the partial resection of a sc teratoma.

Five out of 117 patients who had obtained a macroscopically complete resection and 2 out of 8 who had incomplete resection relapsed at 3–24 months from diagnosis (see Table 2). In 2/7 patients who developed local relapse, malignancy was found at histology.

The patient in whom a biopsy was carried on at diagnosis underwent complete resection of the tumour 6 months later and he is alive without disease 4 years after diagnosis.

Immature teratoma Two out of 56 patients were not valuable: one patient died of a lung malformation a few days after partial resection of a sc teratoma, and one was lost at follow-up.

Eight out of 54 with grade 3 tumours developed disease recurrence 4–24 months after diagnosis (median 9 months): three had sc teratomas and had undergone a macroscopically complete resection in one, incomplete in one and biopsy in one; four had ovarian tumours and had undergone an incomplete resection (three) or a complete one (one); chemotherapy was used in three cases: in one after a complete resection and in two after an incomplete resection. The recurrences were local in seven and distant in one (mediastinal metastases in a sc tumour, grade 3). Malignant cells were found in the specimen of recurrent tumour in three cases.

Table 2 Characteristics of relapsed patients

	Mature teratomas	Immature teratomas
Patients	7/126	8/56
Site of primary T		
Sacrococcyx	5(2)/45	3(2)/19
Ovary	0/35	4(1)/17
Retroperitoneum	1/7	1/2
Mediastinum	1/11	0/3
Surgery		
Comp Res	5(1)/117	2/45
Part Res	2(1)/8	5(2)/10
Biopsy	0/1	1(1)/1
Chemotherapy	–/–	4(1)/8
No chemotherapy	7(2)/126	4(2)/25[a]

In parenthesis cases of malignant relapses

[a] Twenty-five patients did not receive CT for violation of the protocol

T tumour, *Comp res* complete resection, *Part res* partial resection

Table 3 Univariate Cox regression for EFS

Variable	Events *n* (%)	HR (95% CI)	*P*-value
Age (months)			
<18	7 (7.9%)	1	0.507
≥18	9 (10.2%)	1.39 (0.52–3.75)	
Gender			
M	1 (1.8%)	1	0.011
F	15 (12.3%)	7.14 (0.95–50)	
Site of tumour			0.080
SC (64)	8 (12.5%)	1.29 (0.20–5.98)	0.743
Ovary (52)	4 (7.6%)	0.69 (0.12–3.74)	0.663
Testis (34)	–	∞	1.000
Others (19)	2 (10.5%)	1	0.704
Med (14)	1 (7.1%)	0.70 (0.06–7.75)	0.773
Resection			
Complete	8 (5.2%)	1	<0.001
Incomplete	8 (34.8%)	7.70 (2.78–20.0)	
Histology			
MT (grade 0)	7 (5.5%)	1	0.025
IT (grade 1–3)	8 (14.2%)	3.12 (1.15–8.33)	

HR hazard risk, *M* males, *F* females, *SC* sacrococcygeal, *Med* mediastin, *MT* mature teratoma, *IT* immature teratoma

Treatment of relapse

The seven patients with MT and the eight with IT who relapsed underwent a new surgical procedure. The histological examination showed the same features as the primary tumour at diagnosis in five MT and three IT, mature tissue in two cases of primary IT, and teratoma mixed with malignant yolk sac tumour in two primary MT and three IT.

The surgical resection of the relapses was complete in ten and the histology demonstrated non malignant teratomatous tissue: all these patients are alive without evidence of disease at 12–120 months (median 78) from relapse for MT and at 24–144 months (median 96) for IT.

Chemotherapy according to the AIEOP GCT 91 Protocol for Malignant GCT [4] was given to five patients who had malignant tissue at relapse. Two out of the five patients with primary sc tumours (one MT, one IT), who underwent complete resection of the recurred mass and two cycles of CT, are alive without disease at 6 and 11 years from relapse, respectively; one patient, with a primary IT of the ovary, grade 3, who had had an incomplete resection of the relapse, underwent a second incomplete resection, adjuvant chemotherapy and radiotherapy of the residual tumour: the bioptic specimen, obtained at the end of the treatment,

showed fibrotic tissue. This patient is alive and well 10 years after her relapse. Two patients died from progressive disease: an 8 year old girl, with a sc IT, grade 3, who initially had a biopsy, two courses of chemotherapy and an incomplete surgical resection of the residual tumour, and one patient with a completely resected sc MT at birth, who had a relapse 32 months after diagnosis.

Survival and event-free-survival

Overall, 175/179 valuable patients (122 MT, 53 IT) are alive. One hundred and sixty-two patients (116 MT, 46 IT) are alive in continuous complete remission with a median follow-up of 56 months (range 8–144); 13 out of 15 patients who relapsed (six with MT, seven with IT) are alive without evidence of disease 12–120 months after relapse (median 78) for MT and 24–144 months (median 96) for IT. Four patients died, two due to the associated malformation and two for progression of disease; three patients were lost to follow-up. Sixteen events (15 relapses and 1 death) were considered for EFS (Table 3). Overall EFS and OS at 10 years were 90.4% (95% CI 84.8–94.0) and 98.0% (95% CI 93.9–99.4), respectively. Histology was associated with prognosis, with an increased risk of death or relapse for IT patients (HR 3.12, 95% CI 1.15–8.33, $P = 0.025$) (Fig. 1a). A prognostic role on EFS could not be attributed to age and site of the primary tumour; the female gender appeared instead to be linked to a worse prognosis (sevenfold increase in risk) as well as the incomplete resection (eightfold increase of events) (Fig. 1b, c).

Discussion

In this study, as in others [5–8], MT and IT exhibit a female predominance. Approximately, one third of all patients were aged less than 4 months at diagnosis and the majority of these patients presented sc tumours. It is to be noted that in children aged >4 months the malignancy of teratoma is more frequent than in those <4 months. [6, 9] As in other reports, the ovarian tumours occurred in older children [5, 7, 10, 12].

Recently Schneider et al. [12] analysed the features of 1,442 patients with GCT: they found a bimodal age distribution with a first peak in infancy and a second after puberty. While at birth almost all tumours were teratomas in extragonadal site, the most frequent forms in adolescents were germinomatous gonadal tumours; our series of 183 cases show similar features.

Eight children had associated congenital malformations or chromosomal syndromes: Mann reported 8/125 children having malformation with teratoma [9]; an association of presacral teratoma and anal malformation was observed by Ashcraft et al. [13] and by Currarino [14]. A classical association is represented by Currarino syndrome, which includes teratoma, anorectal malformation and sacral malformation. Other Authors report congenital malformations suggesting genetic involvement of teratoma.

Concerning the treatment and outcome, a complete surgical resection is the adequate therapy for patients with teratomas [5, 7].

However a relapse may be observed, even after a complete resection, and this may be characterized by a malignant histology [7, 10, 11, 15, 16].

The relapses were generally more frequent after incomplete resection of sc and ovarian MT or IT. We had five local relapses in the setting of patients with MT, who had undergone a macroscopically complete resection. It is probable that surgical procedure had left some microscopic residual tumour. A malignant recurrence was found in five cases, mostly in sc tumours; one malignant recurrence was observed in the ovary, where a macroscopic residual had been left at the initial surgery. Half the patients treated with chemotherapy relapsed. Mann [7] suggests that in the sacrococcygeal region it is possible that some microscopic malignant elements may remain after an apparent complete surgical resection [7] and are not seen at the pathology analysis. These foci may be responsible for a malignant relapse after an apparent complete resection.

The efficacy of chemotherapy in avoiding malignant transformations of non-malignant tumours is controversial [5, 17, 18]. The POG study [10] analysed the central pathology review of 73 cases which were defined by the local pathologist as IT: 50 patients were confirmed to have pure IT, whereas 23 had microscopic foci of malignant elements; overall, four patients with extragonadal tumour and one with ovarian tumours recurred following chemotherapy (4–6 cycles of PEB); all are alive without disease with a 3-year EFS of 93% (95%CI 86–98%). The authors conclude that the surgical resection and a careful follow-up were efficacious for the cure of patients with IT.

Cushing et al [5] report that the ''wait and see'' approach, after a complete surgical resection of IT was a safe strategy because patients who develop malignant recurrent disease can undergo successful salvage chemotherapy (96.7% DFF).

Some other investigators [11, 15] proposed adjuvant chemotherapy for patients with IT. It has to be noted

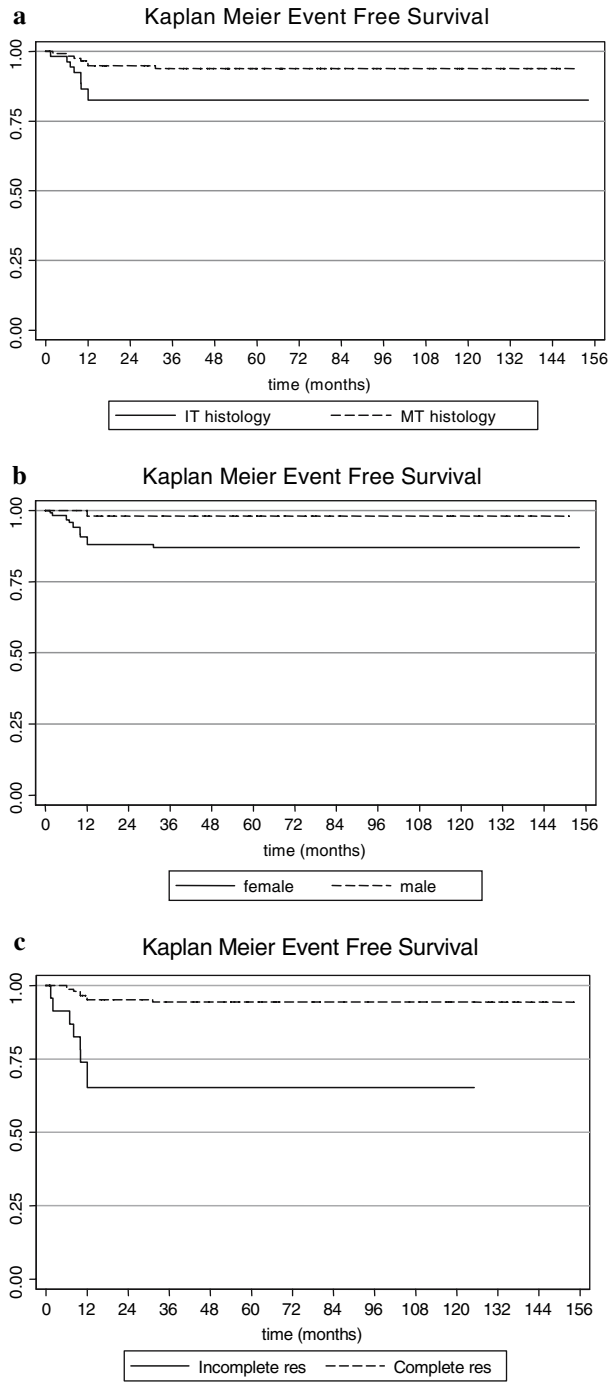

Fig. 1 Kaplan Meier event free survival

that a strategy characterized by the surgical excision and a ''wait and see'' approach is sufficient for patients affected by stage I malignant germ cell tumours [19–24]; consequently it is not reasonable to administer chemotherapy in all the cases after a complete resection of any grade of teratoma.

In the series described by Gobel et al [16], none of the 40 patients with incompletely resected IT treated with chemotherapy developed a malignant recurrence. However the Authors conclude that a larger number of patients are needed to confirm these data.

Rescorla et al. [15] suggests the use of chemotherapy if the αFP level is elevated or in case of residual disease after surgery. In our series αFP was within the normal range, according to the age, in all patients, but four; the tumours, localized in the ovary, were grade 2 or 3, and 1/4 had a relapse; the number of patients was too small to understand the role of an elevated αFP.

In our series, 7/126 MT and 8/56 IT (grade 3) recurred; in 2/7 and 3/8 the relapse was malignant. It seems that immature elements are more frequently at risk of relapse.

The incomplete resection, the histology and the female gender are relevant risk factors for long-term events. However, due to insufficient power, we could not fit a multivariate Cox model to show the independent role of the three identified risk factors.

Concerning the efficacy of chemotherapy, it has to been noted that one of the eight patients treated with CT, had a malignant relapse; however, as described above, in this last patient it is possible that microscopic occult foci of yolk sac tumour had been present since the first diagnosis, which was obtained with a bioptic specimen. The patient did not respond to chemotherapy.

The number of our patients treated with chemotherapy is too small, and little can be said about the value of this treatment in our series. Gobel et al. [11] found malignant elements in partially resected MT and IT, mainly in the sacrococcygeal and ovarian sites [23]. Our data are in agreement with these findings; particularly, the incomplete resection seems to be the principal risk factor for a relapse [15, 16, 24]. In our opinion the adjuvant chemotherapy might be useful in partially resected IT, because the microscopic foci of malignant tissue can be present in the residual mass. Concerning the MT, only two out of 126 cases had a malignant relapse: one of those after a complete resection. It seems reasonable to indicate a very close, long-term follow-up with markers evaluation also in MT, especially if partially resected.

In conclusion, from our study we have observed that histology can be considered a significant prognostic factors; sex and incomplete surgical resection appeared the most important risk factors for malignant relapse and poor outcome. Our data do not demonstrate the efficacy of chemotherapy, because most patients did not receive any adjuvant chemotherapy, in spite of the protocol guidelines. However, since incomplete resection entails the risk of a malignant relapse, it is our opinion that adjuvant chemotherapy might be useful in

partially resected IT. The study of a consistent number of patients could be useful to show the best strategy for these tumours.

Acknowledgments This work was partially supported by MIUR 2003 funds

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