Appendiceal Neuroendocrine Tumours in Childhood: Italian TREP Project

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ABSTRACT

Background: Neuroendocrine tumours (NETs) of the appendix are slow-growing tumours and, although rare, they are the most common gastrointestinal epithelial tumours in childhood and adolescence. The treatment and the follow-up screenings have not been standardised. In addition to this, although tumour size is considered the main prognostic variable to define the aggressiveness of approach, a precise cutoff needs to be established.

Methods: A total of 113 patients younger than 18 years with a diagnosis of appendiceal NETs were registered as of January 1, 2000, until May 30, 2013, within the Rare Tumors in Pediatric Age (TREP) project, an Italian multi-institutional network dedicated to rare tumours in children and adolescents. The recommendations of the Rare Tumors in Pediatric Age study included imaging and laboratory investigations. The treatment after appendectomy was decided on the basis of histology, tumour size, and imaging; primary reexcision (PRE) was not recommended in completely excised tumours, regardless of tumour size and invasiveness.

Results: A total of 113 of 113 patients had a diagnosis of well-differentiated NETs; in 108 of 113 the tumour was smaller than 2 cm and in 5, larger than 2 cm. Excision margins were free in 111 of 113 patients. In 3 of 113 a PRE was performed, and in 1 residual tumour was detected. All 113 of 113 patients are alive in complete remission (median follow-up of 41 months).

Conclusions: Reported data and our experience showed that no relapse or death occurred in children and adolescents affected by appendiceal NETs. Appendectomy alone should be considered curative for most patients, and a more aggressive surgical approach is warranted in the cases with incompletely excised tumours.

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Carcinoid tumours are rare, slow-growing tumours, arising from the enterochromaffine (Kulchitsky) cells disseminated throughout the gastrointestinal (GI) tract and bronchopulmonary system (1), classified by the World Health Organization (WHO) (2) as neuroendocrine tumours (NETs). Besides the GI tract and lower airways, these tumours rarely occur in other sites, such as pancreas, thymus, and ovaries. Although rare in children and adolescents, NETs are nevertheless the most common GI epithelial tumours in this age group (3) and are usually an incidental finding at histology after appendectomy (4,5). Several paediatric series have been reported, but the precise incidence in relation to the total number of appendectomies is not available. A summary of all publications, reporting more than 350,000 appendectomies, yields a frequency of 2 to 5 cases per 1000 appendectomies (6,7). The general incidence has been reported in a range between 1:100,000 and 1.14:1 million children per year (5,8–10).

The diagnostic workup and treatment for these tumours, especially when occurring in children, have not yet been standardised. Although tumour size is considered the main prognostic variable to define the aggressiveness of treatment approach, it remains to be established a precise cutoff to lead to a treatment more intensive than the simple appendicectomy. Moreover, some authors have suggested that the aggressive therapy generally indicated in adults may be not justified in young patients (4,11,12).

In Italy, NETs of the appendix in children have been prospectively registered within the Tumori Rari in Etá Pediatrica (TREP) project, an Italian multi-institutional network dedicated to rare tumours in children and adolescents, which was launched in 2000 under the auspices of the Italian Association of Pediatric Oncology and the Italian Society of Pediatric Surgery (13). Besides the registration of cases, the aim of the project was to help physicians in approaching rare neoplasms through shared diagnostic and therapeutic recommendations, drafted according to the most recent literature.

The present article describes clinical data and treatment results of all of the patients affected by NETs of the appendix, enrolled in the TREP study.

METHODS

Patients younger than 18 years with a diagnosis of "rare paediatric tumours" were centrally registered as of January 1, 2000, at the TREP Data Center (Clinical Trials and Biostatistics Unit, Istituto Oncologico Veneto, Padova, Italy).

Specific printed forms (clinical findings, histopathology, diagnostic workup, therapy, and follow-up) were used for data collection. Tumour size, grading, vascular and perineural invasion, and tumour extension were retrieved from the original histological report, and in selected cases histological review was performed.

All of the patients, or their guardians, gave informed consent for their involvement in the TREP study. Details including clinical features, treatment modalities, and outcome were centrally reviewed for this analysis. The TREP project obtained the approval from the local ethics committee.

The recommendations of the TREP study included that, after the diagnosis of NET, all of the patients were investigated with chest radiography, abdominal ultrasound (US), and Octreoscan (Mallinckrodt, Maryland Heights, MO), a total body scintiscan with ^{111}indium-labelled Octreotide. The determination of specific markers, in particular serum serotonine and urinary 5-hydroxyindoleacetic acid (5-HIIA), was also advocated, also the determination of neuroendocrine markers, such as chromogranin A and neuron-specific enolase (NSE), if possible. In case tumours are larger than 2 cm, further investigations consisted of abdominal computed tomography (CT) scan or magnetic resonance imaging (MRI). The treatment after appendectomy was decided on the basis of the histology and imaging reports.

Primary reexcision (PRE) was not recommended in completely excised tumours, smaller than 2 cm, even in those invading serosa and/or periappendiceal fat, except in the case of microscopic/macroscopic residue on the margins of the appendix. In these patients, the surgical treatment consisted of the caecum resection and pericaecal node biopsy. For tumours larger than 2 cm, the decision to perform the right hemicolectomy, traditionally recommended in the literature, was left to the physicians in charge; however, the group tended to discourage this major procedure, unless positive margins were present. If the imaging demonstrated other suspicious lesions, especially if positive at Octreoscan, our approach was an exploratory laparotomy/laparoscopy with biopsy or a removal of these lesions (Fig. 1).

The follow-up, either in children who have undergone a second surgical procedure or in the others, consisted of a clinical evaluation, abdominal US, and urinary 5-HIIA determination every 6 months for the first 2 years after diagnosis, and then once per year for at least 10 years. A further Octreoscan was suggested in cases of alteration of 5-HIIA or suspicious lesions seen at US.

RESULTS

Between January 2000 and May 2013, 749 cases of ''rare paediatric tumours'' were registered in the TREP database; 113 cases had a diagnosis of carcinoid of the appendix.

Clinical Features

The group of patients included 72 girls and 41 boys, with an age range of 9 months to 17 years (median 12 years). In all of the patients, the diagnosis of NET was obtained at pathological examination after appendectomy for appendicitis or occasional appendectomy during other major surgical procedures (ovarian torsion in 1 case and removal of an ovarian mass in 2).

Most of the patients (91/113) had symptoms related to acute appendicitis (abdominal pain, fever, and vomit). Seven had a history of chronic abdominal pain, 2 referred as having diarrhoea and flushing. No association with genetic syndromes was detected in this series.

Pathological Features

All of the patients had a diagnosis of well-differentiated neuroendocrine tumours. Acute appendicitis was confirmed in 76 cases, in 19 there were no signs of acute inflammation, and for 18 patients data were not available.

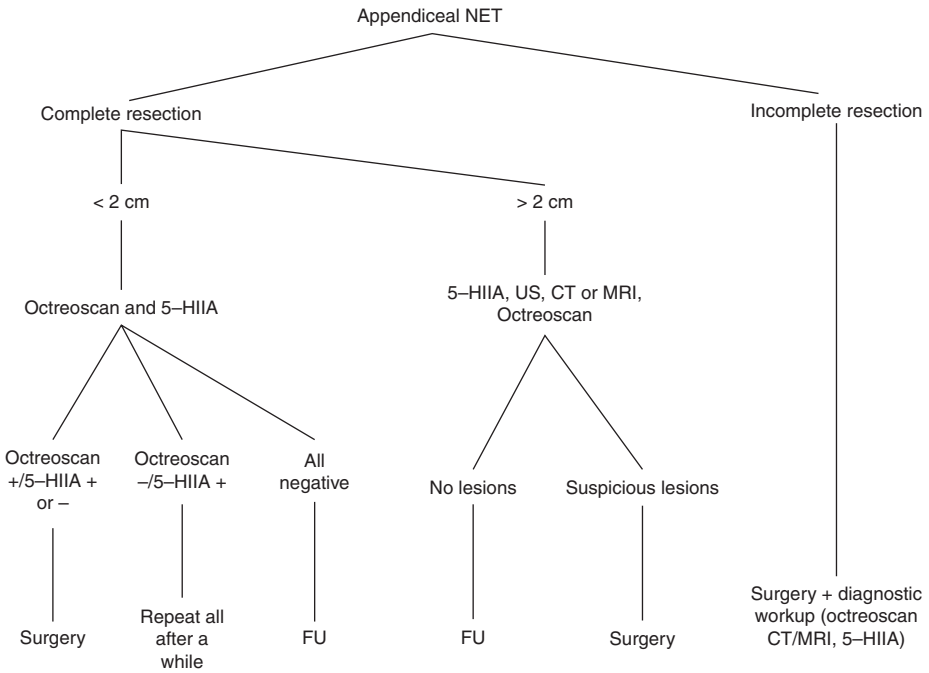

FIGURE 1. Tumori Rari in Etá Pediatrica (TREP) guidelines for diagnostic workup and treatment after appendectomy. CT = computed tomography; FU = follow-up; 5-HIIA = 5-hydroxyindoleacetic acid; MRI = magnetic resonance imaging; NET = neuroendocrine tumour; US = ultrasound.

In 108 patients, the tumour was smaller than 2 cm and in 5, larger than 2 cm (mean 0.7 cm, median 0.5 cm, range 0.1–3 cm). The extension of the tumour beyond the appendiceal wall was observed in 35 cases; in 5 the tumour invaded the serosa and in 28 involved the mesoappendix and periappendiceal fat. In only 2 of 113, data about local invasiveness were not available. The tumour site was described on the pathological report in 75 of 113 cases; the tip of the appendix was the most frequent localisation (62), followed by the midportion (11) and base (2).

The tumour grading according WHO classification of appendiceal NET were evaluated at the diagnosis or after the review (or on the basis of the original histological report when histopathological specimen were not available) in 88 of 113 patients: 84 of 113 were in the category G1 and 4 of 113 were G2; 25 of 113 patients remained unclassified. It is, however, remarkable that all of the patients evaluated according the previous WHO classification (14) were originally classified as well-differentiated, low-grade, classic carcinoid tumours.

The excision margins were free of tumours in 111 of 113 patients, and in 2 the tumour involved the base of the appendix. Microscopic residuals were suspected in the circumferential margin. In 2 patients (both with tumours <2 cm), regional lymph nodes were included in the surgical specimen at the time of appendectomy, and they did not show any pathological feature other than reactive proliferation. In 5 cases, a concomitant parasitic infection of the appendix (1 *Schistosoma haematobium* and 4 *Enterobius vermicularis*) was observed.

Postsurgical Assessment and Further Treatment

Patients With Tumors Smaller Than 2 cm

Abdominal US was performed in 103 patients, chest radiography in 50, abdominal CT scan in 23, and abdominal MRI in 5. CT scan was doubtful in 3 patients and MRI in 2.

The determination of 24-hour urinary 5-HIIA was the main laboratory diagnostic text and was performed in all of the patients. The determination of serum chromogranin A was performed in 53 patients, urinary serotonin in 16, serum NSE in 10, and urinary 5-hydroxytryptophan in 5. 5-HIIA was altered in 3 patients, and serotonine, chromogranin A, and NSE were altered in 3, 2, and 2 patients, respectively.

Seven of 8 patients, with alterations of CT scan/MRI or of serum/urinary markers, were further investigated, both with radiological and laboratory tests without detecting any sign of residual disease (Table 1).

Octreoscan were altered or doubtful in 7 of 76 patients and in all of the patients the test was repeated; in 4 of 6 the second Octreoscan was not significant and in 3 the test result was positive; therefore, a second surgery was decided upon, considering also the positivity of the other radiological or laboratory tests. The first patient had liver lesions detected by CT scan and MRI, with negative 5-HIIA; the lesions were removed with the help of intraoperative US, and a diagnosis of focal nodular hyperplasia was obtained. The second patient, who had positive serotonine and 5-HIIA, had a pericaecal node with micrometastasis, which was completely removed (right hemicolectomy [RHC] was not performed). The third, who had negative 5-HIIA and serotonine, underwent a right hemicolectomy with no tumour detected in the bowel excised and even in none of 30 mesenteric lymph nodes at microscopic examination.

Twenty-eight patients were not investigated with Octreoscan because of the decision taken by the centre, and in 5 cases data were not available. The only patient with microscopic residuals (tumour size 0.9 cm) did not undergo a second surgery on the basis of negative imaging and laboratory screening.

Patients With Tumors Larger Than or Equal to 2 cm

Four of 5 underwent abdominal CT scan, and 1 of 5 undergone MRI. The chest radiography was performed in 3 cases; in 1 case 5-HIIA was initially slightly elevated, but normal at the following evaluation. Octreoscan was negative in all of the patients.

TABLE 1. Patients with altered postsurgical tests

Patients	Tumour size, cm	Histological features*	Altered markers	Altered imaging	Octreoscan	2nd Octreoscan	2nd surgery/other	Outcome (FU)
M, 153	0.5	CE	Serotonine	None	Negative			CR (42)
M, 97	0.5	CE	Chromogranin A	None	Negative			CR (6–lost)
M, 155	0.7	CE mesoappendix	None	CT	Doubtful	Negative		CR (89)
M, 121	0.5	CE	5-HIIA	None	Negative			CR (102)
F, 136	0.3	CE	None	CT, MRI	Positive	Positive	FNH	CR (144)
F, 114	<2	CE	NSE	None	Negative			CR (102)
F, 163	2.2	CE mesoappendix	5-HIIA	None	Negative			CR (105)
M, 123	<2	CE	None	CT, MRI	Doubtful	Negative		CR (60)
F, 157	0.9	CE mesoappendix	5-HIIA, serotonine	None	Positive	Positive	Node excision (micrometastasis)	CR (87)
M, 156	<2	CE	NSE	None	Negative		2nd tumor: Hodgkin disease	CR (39–lost)
M, 133	0.4	CE	Chromogranin A	None	Negative			CR (55)
F, 123	1.12	CE mesoappendix	Serotonine	None	Doubtful	Negative		CR (31)
F, 177	1	CE serosa	None	CT	Negative			CR (84)
F, 215	1.6	CE mesoappendix	None	None	Doubtful	Negative		CR (22)
F, 215	<2	CE	None	None	Doubtful	Doubtful	RHC§	CR (40)

CE = complete excision; CR = complete remission; CT = computed tomography scan; FNH = focal nodula hyperplasia; FU = follow-up; 5-HIIA = 5-hydroxyindoleacetic acid; MRI = magnetic resonance imaging; NSE = neuron-specific enolase; RHC = right hemicolectomy.

* Extent of surgery, level of invasion.

§ Negative at pathological examination.

The only patient with microscopic residual underwent excision of the caecum, and the pathological report did not show any tumour residual.

Outcome

All 113 of the 113 patients are alive in complete remission, with a median follow-up of 41 months (range 1–151 months); 5 were lost at follow-up in complete remission. The patient with positive node is alive and free of disease 87 months after diagnosis.

Three patients later developed a second neoplasm: 1 Hodgkin lymphoma, 1 ovarian mature teratoma, and 1 fibroadenoma of the breast, respectively. In 1 girl, the appendiceal NET was a synchronous tumour detected at laparotomy for a borderline serous cystadenoma of the ovary.

DISCUSSION

The present series represents the first reported prospective national-based cooperative series of carcinoids of the appendix in children, collected in a short period. The present study demonstrated the feasibility of prospective national collaboration even on rare tumour of childhood. A previous TREP study focusing on the comparison between observed cases and cases expected to be seen in Italy according to epidemiological data, demonstrated the ability of the project to recruit virtually all cases of appendiceal NET occurring in children younger than 14 years. In adolescents, about one-third of the cases were instead registered, confirming what ascertained for other rare and more common tumours (13,15). The same article attempted to define the incidence of the tumour, that is, 0.2 cases per million people per year for children of age 5 to 9 years, 1.1 for 10 to 14 years, and 2.5 for 15 to 17 years (15).

Our series confirmed the finding—already reported by others—that well-differentiated NETs of the appendix in childhood generally have a benign course, with an overall survival rate of 100% (9,16) and no cases of tumour-related death reported so far (4,16,17). This may also be related to the evidence that few cases presented with tumours larger than 2 cm, which are theoretically at higher risk for metastatic spread (3,12).

The evaluation of specific markers along with a careful research of possible other lesions is considered mandatory, before deciding the best following treatment. The specificity of urinary 5-HIIA has been reported to be up to 88%, but its sensitivity does not reach 50% (18); therefore, the contemporary determination of serum chromogranin A, whose sensitivity is reported to be up to 65% to 70%, is suggested to possibly reduce the rate of false-negative results (19,20). Among our patients, altered levels of 5-HIIA and chromogranin A were detected in 4 and 2 cases, respectively, but in 1 case only this finding was associated with a positive Octreoscan allowed the recognition of a metastatic node. The Octreoscan has been proved to be a valid tool in the diagnosis of relapse and metastatic disease in adults; however, it must take into account that it does not give information about the amount of residual disease, Moreover, its sensitivity seems to be reduced in lesions smaller than 1 cm (19), and false-positive results are also possible (up to 10%) (21,22). The benign clinical course in children would suggest that the use of Octreoscan in children should be most likely confined to patients with tumours larger than 2 cm, high levels of 5-HIIA, or when a relapse is suspected (Fig. 2). In case of small tumours, patients should avoid an unnecessary exposure to radiation. In our series of 81 Octreoscan performed (76 in patients with tumours <2 cm), 7 were altered but 6 were false-positive and a following Octreoscan in 5 cases and a second surgery in 1 were negative.

Concerning treatment, RHC or caecum resection has been traditionally recommended for tumours larger than 2 cm (23,24); however, it is controversial whether this approach may offer more advantages in terms of overall and event-free survival rates. The

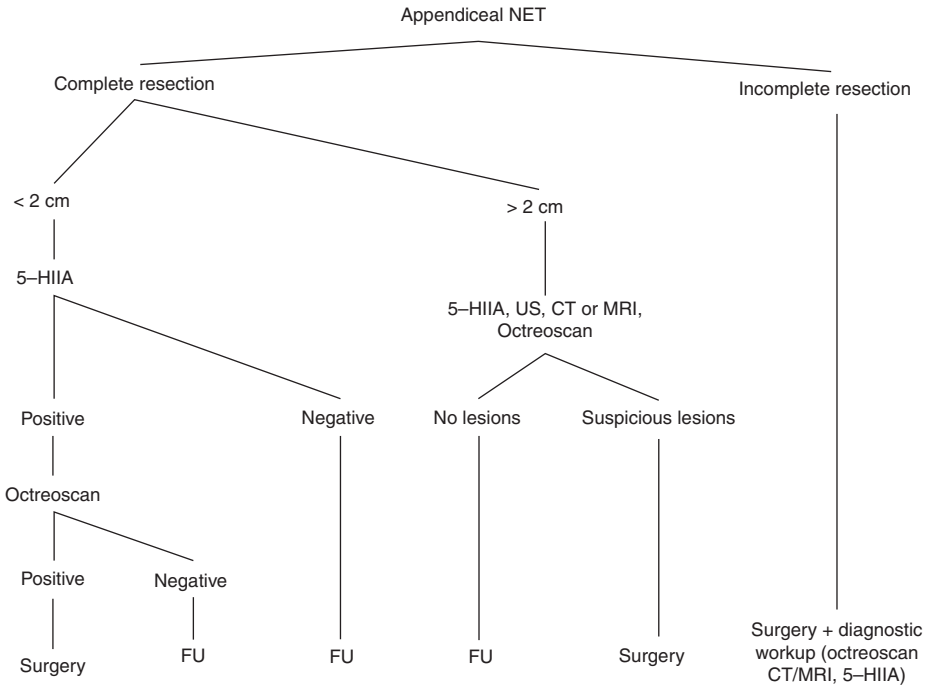

FIGURE 2. New Tumori Rari in Etá Pediatrica (TREP) guidelines for diagnostic workup and treatment after appendectomy. CT = computed tomography; FU = follow-up; 5-HIIA = 5-hydroxyindoleacetic acid; MRI = magnetic resonance imaging; NET = neuroendocrine tumour; US = ultrasound.

most recent guidelines for the treatment of NETs of the appendix in adults (19,20,25) recommend RHC not only for tumours larger than 2 cm but also for incompletely excised tumours of any size, involving the base of the appendix, and for cases presenting vascular invasion or extension into periappendiceal fat. Some authors actually question the need of RHC in case of either vascular invasion or extension into the periappendiceal fat (23,26–29) because in their series no correlation with the presence of distant metastases was observed, albeit, Volante et al (30) observed that worse prognosis was associated with extramural extension (including mesoappendix), well-differentiated carcinoma diagnosis according the 2000 WHO classification, pT3–4 stage, older age, and involving of resection margins, but not with tumour size, mitotic, or proliferative indexes, as considered in the 2010 WHO grading.

Concerning tumour size, Moertel et al (23) found in their own series that 12 of 23 adults with larger than 2 cm tumours did not undergo RHC and just 1 had a relapse 29 years after diagnosis, that was successfully treated with RHC. Other authors recently suggested that RHC did not give any relevant benefit in terms of overall and cancer-specific survival in patients affected by larger than 2 cm NET, being appendectomy alone sufficient for the local control of the disease (27,31–34). In the view of these suggestions and considering the benign clinical course of appendiceal NETs in children, we would question the necessity of aggressive surgery according to the indication given in adults. In the paediatric literature, 2 patients, with a 5-cm and a 0.7-cm tumour, received a secondary RHC because of the size of the tumour in the first case and extension to mesoappendix in the latter, without any further treatment. It has been also observed that no relapse or tumour-related death occurred (9,16,35).

Nonetheless, a recent German article on appendiceal NETs in children and adolescents asserted that all of the patients with tumours larger than or equal to 1.5 cm, even if completely excised, should undergo secondary RHC with mesenteric lymph nodes sampling (17,36). At the basis of their approach, there was a high incidence of micrometastatic nodal spread in 16% of patients (9/60); however, no local or metastatic relapse was observed. Moreover, the real clinical significance of nodal micrometastases is still unclear; whether they represent a true metastatic localisation or not, should be determined on the basis of a larger and long-lasting series.

Among our patients with smaller than 2 cm NET and treated by appendectomy alone, only 1 of 98 presented a nodal spread successfully treated uniquely with a second surgery (2 months after appendectomy). This patient with a micrometastatic nodal localisation had a tumour of 0.9 cm; the persistent alteration of urinary 5-HIIA together with the positivity at Octreoscan caused us to decide upon the further operation.

The data of our case series and those reported in the literature are consistent with the hypothesis that appendiceal NETs in children show benign behaviour and a particularly low propensity to regional node diffusion and metastatic spread, even when they are larger than 1 to 2 cm, or present vascular invasion or extension to mesoappendiceal fat. This is probably related to the fact that in children these tumours are usually well differentiated and are not characterised by a mixed histology (eg, goblet cell carcinoid [GCC], adenocarcinoid) (20). GCC tumours and other less frequent histotypes represent a rare subgroup and their treatment should follow the guidelines in use for adults (37–39). These tumours were not encountered in patients enrolled into the TREP study.

A further interesting finding in our series concerns the occurrence of second tumour in 3 cases (1 Hodgkin lymphoma, 1 ovarian teratoma, and 1 breast fibroadenoma). The association between appendiceal NETs with synchronous and metachronous noncarcinoid malignant neoplasms is well known; in the Surveillance Epidemiology and End Results registry, appendiceal NETs were found associated with neuroendocrine and nonneuroendocrine malignant tumours of the GI tract, lung, and prostate in up to 14.6% of patients (40–42). Such data, together with a less aggressive approach in the management of these neoplasms, could justify a longer follow-up, that, according to some authors, may be lifelong (40–42).

Interestingly, 5 patients showed a concomitant parasitic infection (1 *S haematobium* and 4 *E vermicularis*) of the appendix, and all of them had small-size and well-differentiated tumours (maximum diameter 0.1–0.5 cm, Ki-67 [cell proliferation–associated nuclear antigen] <2% or negative); a proliferation of neuroendocrine cells triggered by a chronic infection as stated for bladder cancer and GCC of the appendix could be hypothesised (43,44).

In conclusion, the study represents a large prospective multicentre paediatric series on appendiceal NETs, aiming to add further data to the existing literature. The final purpose of such analyses should be that of establishing shared diagnostic and therapeutic guidelines (Fig. 2). The reported data may advise that appendectomy alone should be considered curative in all completely resected NETs of less than 2 cm. A more aggressive surgical approach, such as subtotal cecectomy, total cecectomy, or RHC, is warranted in those cases with incompletely excised tumours. Larger series with longer follow-up are needed to establish, if children with appendiceal NETs larger than or equal to 2 cm or node involvement could retrieve a real benefit from secondary RHC. As part of the recently founded European Cooperative Study Group for Pediatric Rare Tumors (EXPeRT), the TREP group is promoting a wide-ranging initiative on paediatric rare tumours, with the objectives of a joint analysis on a large series of European cases and the development of harmonised, internationally recognised recommendations (45,46).

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