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Ewing's tumour family of the soft tissues in children: 11 years of experience of the Polish Pediatric Solid Tumours Group

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Introduction. Peripheral primitive neuroectodermal tumour (PNET) and extraosseous Ewing's sarcoma (EES) are rare paediatric malignancies, which, clinically, are regarded as partially chemosensitive neoplasms.
Material and methods. We performed a retrospective analysis of clinical data collected in the coordinating centre. All patients were under the age of 19 and presented with PNET (36 cases) or EES (8 cases). They were treated according to the CWS-91, SIOP-MMT-91 or CWS-96 protocols. The primary tumour was localized within the head/neck region in 8 cases (18.2%), in 11 cases (25%) within the chest wall, in 3 cases (6.8%) in the abdomen, in 8 cases (18.2%) paraspinally, in 5 cases (11.4%) within the pelvis, and in 9 cases (20.5%) on the extremities. In 10 patients (22.7%) distant metastases were present at the time of diagnosis.
Results. 32 children (72.7%) achieved complete remission with relapse in 16 cases – local failure in 9, distant failure in 3 and mixed in 4 cases. Response to chemotherapy was observed in 83.3% subjects: in 16.7% – complete, in 33.3% – good and in 33.3% – partial. The remaining 16.7% did not respond to chemotherapy. 5-year event-free survival (EFS) and overall 5-year survival estimate (OS) for all analysed patients was 0.39±0.08 and 0.44±0.08, respectively. Patients treated according to the CWS-96 protocol had a slightly better prognosis as compared to children treated according to the CWS-91/SIOP-MMT-91 protocols. Important factors influencing prognosis were gender, disease stage, and tumour localization.

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Conclusions. Tumours localized within the abdomen and the extremities, as well as the presence of distant metastases, are important unfavorable prognostic indicators. Radiotherapy and radical surgery supporting intensive chemotherapy could reduce the risk of relapse.

Rodzina guzów Ewinga w obrębie tkanek miękkich u dzieci: 11-letnie doświadczenie Polskiej Pediatrycznej Grupy Guzów Litych

Wprowadzenie. Obwodowy pierwotny guz neuroektodermalny oraz pozakostny mięsak Ewinga należą do rzadkich złośliwych nowotworów u dzieci. Klinicznie guzy traktowane te są jako częściowo wrażliwe na chemioterapię.
Materiał i metoda. W pracy dokonano retrospektywnej analizy danych klinicznych pacjentów zgłoszonych do ośrodka koordynującego. Wszyscy pacjenci byli w wieku poniżej 19 lat i u wszystkich rozpoznano obwodowy pierwotny guz neuroektodermalny lub pozakostnego mięsaka Ewinga. Leczenie było przeprowadzone w oparciu o następujące protokoły lecznicze: CWS-91, SIOP-MMT-91 lub CWS-96. U 36 osób rozpoznano PNET, natomiast u 8 EES. Guz pierwotny zlokalizowany był u 8 pacjentów (18,2%) w obrębie głowy/szyi, u 11 (25%) w zakresie ściany klatki piersiowej, u 3 (6,8%) w jamie brzusznej, u 8 (18,2%) przyrdzeniowo, u 5 (11,4%) w miednicy, i u 9 (20,5%) w obrębie kończyn. U 10 dzieci (22,7%) w momencie diagnozy stwierdzono obecność przerzutów odległych.
Wyniki. 32 osoby (72,7%) uzyskały całkowitą remisję. Wśród 16 pacjentów, którzy uzyskali pełną remisję, wystąpił nawrót choroby: u 9 stwierdzono wznowę lokalną, u 3 przerzutową i u 4 mieszaną. Po pierwszym cyklu chemioterapii, 83,3% guzów odpowiedziało na zastosowaną chemioterapię: w 16,7% zaobserwowaną pełną odpowiedź, w 33,3% dobrą i w 33,3% częściową. Pozostałe 6,7% guzów nie zareagowało na chemioterapię. 5-letnie przeżycie wolne od choroby (EFS) i całkowite przeżycie (OS) dla wszystkich analizowanych pacjentów wyniosło odpowiednio 0,39±0,08 i 0.44±0,08. Pacjenci leczeni zgodnie z protokołem CWS-96 charakteryzowali się nieznacznie lepszym rokowaniem w stosunku do pacjentów leczonych według protokołu CWS-91/SIOP-MMT-91. Czynnikami wpływającymi na przeżycie były płeć, stadium choroby i lokalizacja ogniska pierwotnego.
Wnioski. Lokalizacja nowotworu w obrębie jamy brzusznej i kończyn, jak również obecność przerzutów odległych były istotnymi niekorzystnymi parametrami rokowniczymi. Radioterapia i radykalny zabieg chirurgiczny, wspomagające chemioterapię, mogą obniżyć ryzyko nawrotu choroby.

Key words: Ewing's sarcoma, peripheral primary neuroectodermal tumour, outcome, children
Słowa kluczowe: mięsak Ewinga, pierwotny obwodowy guz neuroektodermalny, wyniki leczenia, dzieci

Introduction

Peripheral primitive neuroectodermal tumour (PNET) and extraosseous Ewing's sarcoma (EES) account for approximately 10% of all paediatric soft tissue sarcomas [1]. They present as small round cell malignancies of neural crest origin. The tumor cells typically demonstrate expression of MIC2 (CD99) and β2 microglobulin, a presence of neuronal markers (neurospecific enolase – NSE, S-100 protein, neurofilaments and others), and/or form Home-Wright rosettes [1, 2]. Previously the two entities were distinguished basing on immunochemistry and microspopic examination. If tumour cells presented with at least two neuronal markers and/or formed Home-Wright rosettes, the neoplasm was classified as PNET; if there was no or only one neuronal marker, Ewing's sarcoma was diagnosed. Nowadays both tumours are classified as the Ewing's family tumours, as it was shown that they both demonstrate specific chromosomal aberrations: t(11;22) or t(21;22) with formation of specific fusion genes, and show several immunohistochemical reactions typical only for Ewing's family tumours [1, 3].

Clinically, both tumours are regarded as partially chemosensitive malignancies [4-7]. The most common localisations include the trunk, the extremities and the head and neck. The treatment of Ewing's family tumours in children consists of a combination of multi-agent chemotherapy, radiotherapy and surgical removal of the primary tumor [4-7]. Although during the last 20 years a significant improvement of outcome was achieved in this group of patients the mortality rate remains high. Below we present a multicenter study demonstrating our experiences in the diagnosis and treatment of 44 children and adolescents suffering from Ewing's family tumours.

Material and methods

Patients characteristics

The analysed data were collected over a decade, beginning with the year 1991 in institutions collaborating with the Polish Paediatric Solid Tumours Group. At the time of diagnosis the patients were under 19 years of age. In all cases we recognised peripheral primary neuroectodermal tumours or extraosseous Ewing's sarcomas. Institutional ethical review and informed consent were obtained from all patients. The median follow up was 26 months (range: 4 – 117 months) for all patients and 40 months (range: 4 – 117 months) for surviving patients.

Over the study period (1991-2002) 306 children with soft tissue sarcomas were registered at the coordinating centre. Of these 36 (11.8%) presented with PNET and 8 (2.6%) with EES. Their age ranged from 6 to 210 months (mean: 117.2±66 months, median: 124.5 months); 21 subjects (47.7%) were below the age of 10, and 23 (52.3%) were older than 10 years. No gender predominance was observed: there were 22 boys (50%) and 22 girls (50%). Detailed patient characteristics have been presented in Table I.

Table I. Patient characteristics

Characteristic	Number of patients (%)
Total	44 (100%)
Diagnosis:	
– Peripheral primitive neuroectodermal tumour (PNET)	36 (81.8%)
– Extraosseus Ewing's sarcoma (EES)	8 (18.2%)
Treatment:	
– CWS-91 Protocol	13 (29.6%)
– SIOP-MMT-89 Protocol	2 (4.5%)
– CWS-96 Protocol	29 (65.9%)
Age:	
– Median value	124.5 months
– <10 age	21 (47.7%)
– ≥10 age	23 (52.3%)
Gender:	
– Boys	22 (50%)
– Girls	22 (50%)
Tumour localization:	
– Head/neck region	8 (18.2%)
– Chest wall	11 (25%)
– Abdomen	3 (6.8%)
– Paraspinal	8 (18.2%)
– Pelvis	5 (11.4%)
– Extremities	9 (20.5%)
Tumour size	
– <5 cm	9 (20.5%)
– ≥5 cm	33 (75%)
– no data	2 (4.5%)
Tumour stage	
– II (localized disease, microscopic rests after resection)	7 (15.9%)
– III (localized disease, macroscopic rests after resection)	27 (61.4%)
– IV (distant metastases)	10 (22.7%)
Regional lymph nodes involvement:	
– Yes	10 (22.7%)
– No	34 (87.3%)
Metastases localization:	
– Lungs	6
– Bones	3
– Non-regional lymph nodes	3
– Liver	2
– Bone marrow	2
– Pleura	1
– Central nervous system	1
– Right upper arm	1

Treatment

Over the last decade different modalities were applied in the treatment of childhood Ewing's family tumours of soft tissues. In the early nineties (1991-1995) two protocols were in use: the CWS-91 protocol (13 patients) for stage I-III [4] and the SIOP-MMT-89 protocol for stage IV – (2 patients) [5]. From 1996 onward the CWS-96 protocol (29 patients) [6] was used for all patients (Table I). All these protocols present combinations of multi-agent chemotherapy, radiotherapy and primary or/and secondary surgical tumour removal. They all involve combinations of vincristine, actinomycine D, doxorubicin, epirubicine, ifosfamide, cyclofosfamide, carboplatine, cis-platin and etoposide. Combinations of VACA (VCR, ADR, CY, AMD), EVAIA (VP-16, VCR, ADR, AMD, IFO) and CEVAIE (CARBO, EPI, IFO, AMD, VCR, VP16) have been adopted in the CWS protocols and high-dose chemotherapy – Cy/thiotepa and melphalan/VP-16 with hematopoietic stem cell rescue or oral maintenance therapy with VP-16/ idarubicin and trophosphamide have been investigated in metastatic patients. The intensity, duration and type of chemotherapy were stratified according to the risk groups defined basing on histology, site and TNM status. In the CWS-91 subpopulation patients from group A and B received VACA and patients from group C, i.e. with poor prognosis – the EVAIA protocol. In the CWS-96 protocol the chemotherapeutic regimen has been risk-adapted and stratified according to TNM, primary resectability and histology. Patients in the low risk group received only VCR and AMD. Standard risk patients were administered VCR, AMD and IFO (IVA). Patients in the high risk group were administered CEVAIE – six drug cycles. Radiation was an effective method of achieving local tumor control in patients with microscopic or gross residual disease following surgical resection or chemotherapy. Recomendations for radiation depended on the primary site and size, histology, age and the extent of disease before and after surgical resection. Irradiation was avoided in young children (< 3 years), whenever possible, because of its adverse effects on growth. According to the protocols, radiotherapy was commenced during chemotherapy in the 13^{th}–14^{th} week of treatment (CWS-91) or during the 10^{th}–11^{th} week of treatment (CWS-96). Radiotherapy was individually considered in small children (below the age of 4) depending on the response to chemotherapy. The CWS studies recommended accelerated hyperfractionated irradiation (2x1.6 Gy daily). According to the CWS-91 protocol the patients were irradiated with 32 Gy/48 Gy and according to the CWS-96 – with 32 Gy/44.8 Gy. Second-look surgery was stipulated whenever the tumour was considered primarily non-resectable in any imaging technique: computed tomography (CT) or magnetic resonance tomography (MRT). None of the patients had been previously treated for any other malignancy.

Treatment response was evaluated after the first cycle of chemotherapy in all patients with disease stage III and IV If the tumour was not present in any results of imaging diagnostics (CT, MRT or sonography) and all metastatic lesions cleared, the patients were assigned to the *"complete response"* group. Patients with tumour regression down to 1/3 or less of the initial tumour volume were classified as *"good responders"*. Patients with tumour size of less than 2/3 but more than 1/3 of the primary tumour volume were assigned to the *"partial responding"* group. The group of *"non responders"* consisted of all patients with progression or stabilisation of the disease and/or with tumour regression by less than 1/3 of the initial tumour volume.

Relapse

"Local relapse" was defined as recurrence of the disease at the site of the primary tumour. Relapse was considered *"regional"* if the malignancy appeared in the regional lymph node or *"distant"* if it was found in any other localisation. If relapse involved more than one of groups mentioned above, it was considered a *"mixed relapse"*.

Statistical analysis

Data available by May 2002 was analysed using *Statistica® 97 PL* for Windows software. Kaplan-Meier overall survival (OS) was calculated from the onset of therapy until the latest follow-up or death from any cause, Kaplan-Meier event-free survival (EFS) – from the onset of therapy until the time of treatment failure [8]. Failure was defined as relapse or death from any cause. The differences between the curves were estimated by *F* Cox test and p-values less than 0.05 were considered statistically significant.

Results

At the time of analysis 23 subjects (52.3%) were still alive. The detailed outcome analysis according to the disease stage is presented in Table II. 32 children (72.7%) achieved complete clinical remission (CCR) after first line treatment. In 16 individuals, who had achieved CCR (36.4%) relapse occurred: local relapse in 9 cases (20.5%), distant relapse in 3 cases (6.8%) and mixed relapse in 4 cases (9.1%). The remaining 16 (36.4%) pts are still in 1st CCR. In 4 cases (9.1%) partial remission was documented while in 8 cases (18.2%) we noted progression.

Table II. Final outcome according to the stage of disease

	Stage II	Stage III	Stage IV
Surviving patients:	6	12	5
– First complete remission	6	8	2
– Partial remission	–	2	1
– Local relapse	–	1*	1
– Metastatic relapse	–	–	1**
– Mixed relapse	–	1	–
Deceased patients:	1	15	5
– Partial remission	–	1***	–
– Local relapse	–	6	1
– Metastatic relapse	–	1	1
– Mixed relapse	–	2	1
– Progression	1	5	2

* The patient achieved second complete remission
** The patient achieved second complete remission
*** The patient died because of acute brain oedema

After the first cycle of chemotherapy 30 patients with stage III and IV disease were assessed according to treatment response. 5 patients (16.7%) responded completely to the employed treatment, 10 (33.3%) were classified as good responders, in 10 cases (33.3%) partial response was observed, and the remaining 5 children (16.7%) were classified as non-responders.

Radiotherapy was administered to 31 patients (70.5%) – the dose range varying from 22.5 to 58 Gy (mean: 42.2±9.0 Gy). 12 patients received hyperfractionated irradiation and 19 subjects – standard irradiation. The treatment results according to the administered radiotherapy are presented in the Table III. The most common reasons for not administering radiotherapy were: patient age below 4 years or lack parental consent.

Second-look surgery was performed in 17 children (38.6%). In 2 children with stage III disease second-look surgery was limited to biopsy only, which revealed no residual tumour (histological complete remission), and in another patient only the metastases were radically removed, as no residual tumour was discerned on imaging. All these 3 patients remain in first complete remission. In 6 patients mutilating resection of the primary tumour was performed, however only in 2 cases the resection was radical. 1 patient is still alive and in complete remission and 1 (in stage IV) died due to disease progression. In 3 patients microscopic, and in 1 patient macroscopic tumour residue was found; all these patients died: 2 due to local relapse, 1 due to mixed relapse and 1 due to rapid disease progression. Another 8 patients underwent non-mutilating surgery, which was radical only in 3 cases. Unfortunately, all these patients died: 2 because of local relapse and 1 because of metastatic relapse. In 3 patients microscopic residuum was observed (all these patients died) and in 2 cases – macroscopic residue (one patient is still alive in CCR and one died due to local relapse).

5-year event-free survival (EFS) and overall 5-year survival estimate (OS) for all the patients was 0.39±0.08 and 0.44±0.08, respectively. Patients treated according to the CWS-96 protocol had slightly better prognosis as compared to children treated according to the CWS-91/SIOP-MMT-91 protocol (5-year EFS 0.41 and 0.27, respectively, p=0.03; 5-year OS 0.44 and 0.4, respectively, p=0.09). Having analysed several clinical parameters we state that the most important factors influencing

Table III. Final results of treatment according to the administered radiotherapy

	No radiotherapy	Standard radiotherapy	Hyperfractionated radiotherapy
Surviving patients:	5	10	8
– First complete remission	3	6	7
– Partial remission	2	1	–
– Local relapse	–	1	1**
– Metastatic relapse	–	1*	–
– Mixed relapse	–	1	–
Decreased patients:	8	9	4
– Partial remission	1***	–	-
– Local relapse	–	6	1
– Metastatic relapse	1	1	–
– Mixed relapse	–	1	2
– Progression	6	1	1

* The patient achieved second complete remission
** The patient achieved second complete remission
*** The patient died because of acute brain oedema

prognosis are gender (boys vs. girls: 5-year EFS 0.28 and 0.38, respectively, p=0.04; 5-year OS 0.31 and 0.58 respectively, p=0.02), stage of disease (Figure 1), and tumour localization (Figure 2). The best outcomes were observed in patients with stage II disease (stage II vs. stage III: p<0.01; stage II vs. stage IV: p<0.01), and poorer prognosis was found in patients with stage IV disease, although the difference between stage IV and stage III was not statistically significant (p=0.47) (Figure 1). When comparing different tumour localizations the best survival ratio was found in the case of tumours located within the pelvis and paraspinally. Very poor outcome was observed in patients with neoplasms within the abdomen and the extremities – in the case of these localisations we did not observe survivals exceeding 5 years (Figure 2). We observed no impact on survival of

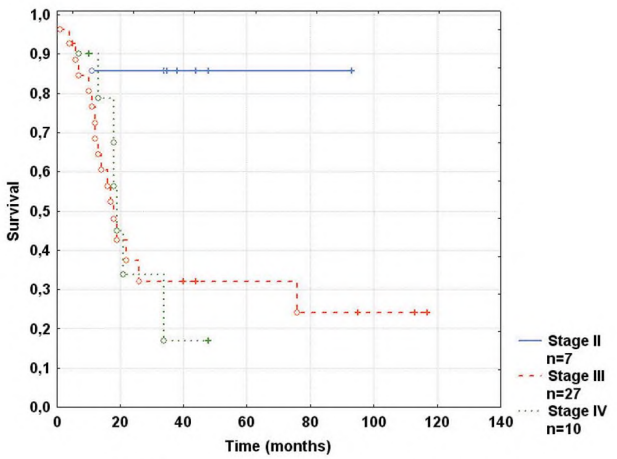

Figure 1. Overall survival according to disease stage

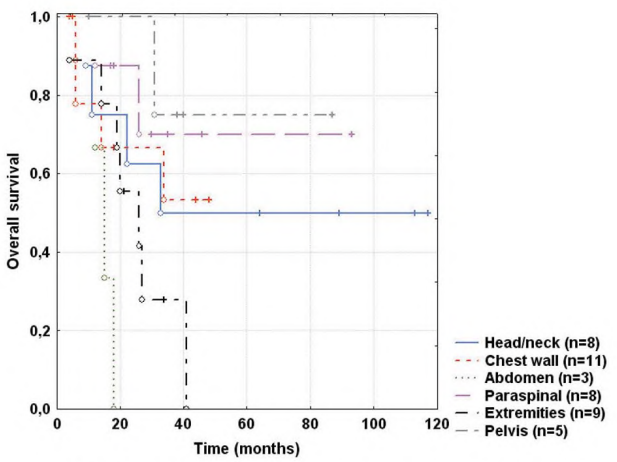

Figure 2. Overall survival according to primary tumour localization

such parameters as: age (<10 years vs. >10 years, p=0.42), diagnosis (EES vs. PNET, p=0.51), tumour size (<5 cm vs. >5 cm, p=0.38) and regional lymph node involvement (involved vs. non-involved, p=0.92).

As for response to the 1st chemotherapy cycle – better outcomes were observed in the case of children showing complete response or regression of over 2/3 of the tumour, as compared to patients who responded only partially or were classified as non-responders although the difference was not significant (Figure 3). In 7 patients with disease stage III and IV we had insufficient data to evaluate the response after the 1st cycle of chemotherapy. Radiotherapy had significant influence on the final results of therapy (Table III, Figure 4). Patients treated with any kind of radiotherapy presented with a significantly better survival ratio as compared to patients who did not receive any irradiation (p<0.05; Figure 4). Although there was no significant difference in the survival of patients who had undergone hyperfractionated and standard radiotherapy, it seems that hyperfractionated irradiation could be more profitable, as in this group the relapses were less common: 4 subjects (33.3%), as compared to 11 patients (57.9%) in standard radiotherapy group (Table III).

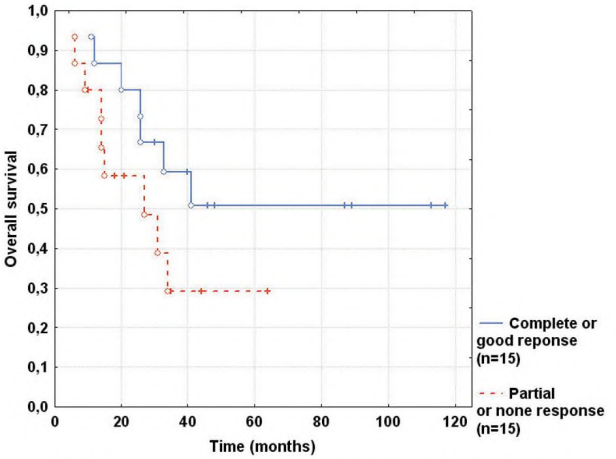

Figure 3. Overall survival according to the response to the 1st chemotherapy cycle in patients with stage III and IV

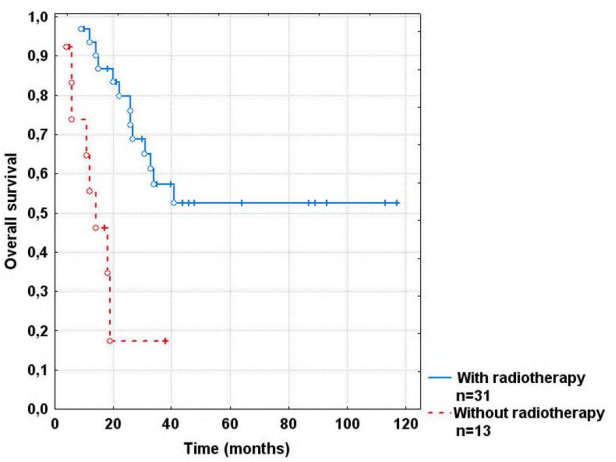

Figure 4. Overall survival according to the performed radiotherapy

Discussion

Ewing's family tumours of soft tissue are rare childhood malignancies (the incidence in Poland is estimated at approximately 4-5 new cases per year). Therefore only the cooperation of many paediatric and oncological centres allows to perform a reliable analysis of patient

data. This study is a multicenter analysis of 11 years of experience of the Polish Pediatric Solid Tumours' Group, which, to the best of our knowledge, is the first such an attempt in Poland.

The characteristics of our patient group are similar to those previously reported in literature [9-13]. The tumours are most common in older children and in young adolescents, although sometimes they occur in very young patients or even in neonates [12]. There is no gender predominance. The most common locations are: the chest wall, the extremities and the head and neck region. Distant metastases predominantly involve the lungs and bones. However, it seems that in Polish children and adolescents the diagnosis was made relatively late, thus resulting in a more advance patients status. In most patients primary tumours were over 5 cm (75% in this study, as compared to 63% in the American group [11]). Moreover, radical primary resection was not possible in any patient and thus we enrolled no patients in stage I of the disease – i.e. in the group with the best survival ratio [11, 12]. Similarly, the percentage of subjects in stage II was also lower (16%) than in other studies (23-27%) [11, 12].

The more advanced stage of the disease could result in the poorer survival ratio of our group (5-year EFS 39% and 5-year OS 44%) as compared to that reported by other authors (EFS 55-67%, OS 62-77%) [11, 13]. Although the complete remission ratio was high (over 70%) and comparable to that reported in literature, yet the incidence of relapses (especially local) was very high. This could be explained by the fact that a relatively large group of patients (nearly 30%) were not irradiated. We have clearly demonstrated that radiotherapy is an important element in the therapy of PNET and EES and significantly improved prognosis. Our observations are consistent with those of other authors [11, 14-16]. Interestingly, second-look surgery did not improve local control; this, in turn, contradicts literature data, according to which complete surgical excision reduces the risk of local reccurence, although it does not prevent metastatic spread [12]. However, in our patient group a majority of the resections were incomplete – with microscopic, or even macroscopic, tumour residue. Moreover, the excision was predominantly performed in patients who showed poor response to chemotherapy, and therefore were at an increased risk of progression.

The stage of disease, gender and tumour localization were the most important factors affecting survival. Parameters such as tumour size and patient age had no impact on survival. We found this surprising, as these latter parameters are an element of the stratification of patients in the new CWS-2002P protocol [7]. Although our observations are similar to those reported by other authors, who had also stressed the importance of tumour localization and disease stage as the most important predictive values [11-13], yet some differences do meet the eye. Raney et al. [11] have reported the region of the head and neck, as well as the extremities, as the more favourable tumour locations. Zogopoulos et al. [13] have reported that tumours localized within the extremities had had the best prognosis, while in our study tumours located on the extremities had the worst outcome. Moreover, in the study of Zogopoulos et al. [13] patients with primary pelvic tumours achieved very poor survival, while in the case of our study material this group had the most favourable outcome. Although our group is relatively small, this observation may suggest that our patients had, in fact, represented another population of children. Additionally, although Zogopoulos et al. have identified gender as a significant prognostic parameter, longer survivals characterised the boys (boys vs. girls survival ratio: 78.5% vs. 52.1%; p=0.007). In our group, boys had a less favorable outcome and we have failed to find any explanation for this discrepancy. As has already been demonstrated [17], we have confirmed that there were no significant differences in survival between EES and PNET.

The cooperation of Polish centres for paediatric oncology has resulted in the unification of the treatment modalities applied in the case of soft tissue sarcomas in children. A significant improvement in survival was noted after the introduction of new protocol – the CWS-96. We do hope, that new CWS-2002P protocol [7] will result in further improvement of prognosis in Polish children suffering from EES or PNET. The introduction of maintenance chemotherapy after intensive chemotherapy, which the CWS-96 protocol provides for patients with distant metastases, could further improve survival in patients with PNET and EES. This may be supported by the results obtained in IRS groups [11], where a majority of patients are treated for a long period of time (81% of individuals were treated for 2 years). Moreover, the introduction of a new treatment option could further improve patient prognosis [18-20].

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