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# Endocrine sequelae after treatment for childhood medulloblastoma

Powikłania endokrynologiczne po zakończeniu leczenia medulloblastoma u dzieci

## ABSTRACT

**INTRODUCTION.** Endocrine abnormalities in children after treatment for medulloblastoma (PNET, primitive neuroectodermal tumour) may concern one or more hormones and may appear at different periods of time following therapy.

**MATERIAL AND METHODS.** The examination was performed on a group of 23 children (age 1–18 years) treated for medulloblastoma/PNET by neurosurgery, radio-, and chemotherapy (22 children), or neurosurgery with chemotherapy (1 child). Before the initiation of the therapy, auxological measurements and hormonal investigations were performed. Three children died during the therapeutic process. For the rest, the examinations were repeated every 3–6 months for the 3 years after completion of the treatment.

**RESULTS.** No pre-therapy abnormalities were noted in the analyzed group. In the first 3 years after medulloblastoma treatment endocrinology disorders were found in 8 patients. Five patients presented with a single disorder, 2 patients had 2 abnormalities, and 1 patient manifested 3 disorders. Decreases in growth velocity (in 7), including growth hormone deficiency (in 4) primary hypothyroidism (in 3), hypogonadotropic hypogonadism (in 1), and osteoporosis (in 1), were found. Decreases in height velocity appeared 4–24 months after the treatment, and hypothyroidism after 7–34 months. Hypogonadism was the first complication, observed

3 months after treatment, and osteoporosis was noted 19–24 months after medulloblastoma treatment.

**CONCLUSIONS.** Children, after radio- and chemotherapy for medulloblastoma/PNET, are a group at risk of developing late endocrine complications. We suggest the protocol of long-term follow-up medulloblastoma survivors, based on clinical symptoms and hormonal and radiological examinations.

**Key words:** medulloblastoma/PNET, children, endocrine sequelae  
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## STRESZCZENIE

**WSTĘP.** Zaburzenia endokrynologiczne po leczeniu medulloblastoma/PNET (*primitive neuroectodermal tumours*) u dzieci mogą dotyczyć wydzielania jednego lub kilku hormonów i występować w różnym okresie od zakończenia terapii.

**MATERIAŁ I METODY.** Badaniu poddano grupę 23 dzieci w wieku 1–18 lat leczonych z powodu medulloblastoma/PNET z zastosowaniem operacji neurochirurgicznej, a następnie radio- i chemioterapii (22 dzieci) oraz operacji neurochirurgicznej z następującą chemioterapią (1 dziecko). Przed rozpoczęciem leczenia u wszystkich dzieci przeprowadzono pomiary auksologiczne oraz badania hormonalne. Troje dzieci zmarło w trakcie leczenia. U pozostałych badania powtarzano co 3–6 miesięcy przez 3 lata od zakończenia leczenia.

**WYNIKI.** W grupie 23 dzieci przed rozpoczęciem leczenia nie obserwowano żadnych zaburzeń. W pierwszych trzech latach od zakończenia leczenia z powodu medulloblastoma/PNET zaburzenia wystąpiły u 8 pacjentów. U 5 były to pojedyncze zaburzenia, u 2 wystąpiły dwa zaburzenia, a u 1 pacjenta trzy zaburzenia. Obserwowano: zwolnienie szybkości wzrastania (u 7) z niedoborem

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hormonu wzrostu (u 4), pierwotną niedoczynność tarczycy (u 3), hipogonadyzm hipogonadotropowy (u 1) oraz osteoporozę (u 1). Zwolnienie szybkości wzrastania wystąpiło w okresie 4–24 miesięcy po zakończonym leczeniu, niedoczynność tarczycy w okresie 7–34 miesięcy, hipogonadyzm pojawił się najwcześniej, bo już po 3 miesiącach od zakończenia leczenia, a osteoporoza w okresie 19–24 miesięcy.

WNIOSKI. Dzieci poddane radio- i chemioterapii z powodu medulloblastoma/PNET stanowią szczególną grupę ryzyka późnych powikłań endokrynologicznych. Wskazuje to na konieczność stworzenia protokołu długoterminowego monitorowania tych pacjentów opartego na objawach klinicznych, badaniach hormonalnych i radiologicznych.

**Słowa kluczowe:** medulloblastoma/PNET, dzieci, powikłania endokrynologiczne

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## Introduction

Medulloblastoma is the most frequent primary brain tumour in children, accounting for as much as 10–20% of central nervous system (CNS) solid tumours, and approximately 40% of all posterior fossa tumours [1–3]. It may appear at any age, but  $\frac{3}{4}$  of all medulloblastoma cases are observed in children. The highest rate of incidence is in the age range 3–5 years. It is more common in boys than in girls (1.5:1) [1, 5]. Medulloblastoma is a poorly differentiated, highly malignant, highly invasive neuroepithelial embryonal tumour with a high propensity to disseminate in the whole CNS [1]. Together with pineoblastoma, ependymoblastoma, retinoblastoma, neuroblastoma and esthesioneuroblastoma, medulloblastoma belongs to the group PNET (primitive neuroectodermal tumours).

Current treatment for medulloblastoma includes surgery with the following adjuvant chemotherapy (in children under 3 years of age), regardless of the extent of the procedure, and adjuvant chemotherapy with craniospinal radiation in children over 3 years of age [1]. There is a high risk of late consequences in patients after medulloblastoma treatment, which is caused by tumour treatment, as well as a risk of relapse. Mortality rates due to medulloblastoma are 15 times higher compared to the normal population. Late consequences caused by brain irradiation may include: endocrine disorders, impaired or destroyed hearing, and mental retardation.

There is a positive correlation between the total dose of radiation, the way of fractionation, and the dysfunction of the hypothalamo-pituitary axis [1]. For this reason, there is a tendency to reduce the dose of irradiation to limit its adverse effects, at the same time main-

taining treatment efficacy [1]. Another cause of late endocrine post-therapeutic complication may also lie in chemotherapy.

Depending on the local medical centre, there are different protocols for monitoring potential endocrine consequences of childhood medulloblastoma. To date, there is no universal protocol in our country.

## Objective

The objective of the current investigation was to examine the impact of the treatment for childhood medulloblastoma/PNET on the incidence of the late endocrine consequences in children and adolescents following completion of therapy, as well as an attempt at developing a protocol for detection of such complications.

## Material and methods

The prospective investigation included 23 children (9 girls, 14 boys) aged 1–18 years treated for medulloblastoma/PNET. Two of them died during the therapy and another died after 3 years because of recurrent disease. Before the initiation of the therapy, in all cases, auxological measurements (body weight, growth velocity, nutritional status) and hormonal investigations: ACTH, cortisol, TSH,  $fT_4$ ,  $fT_3$ , IGF-1, LH and FSH, were performed. All the children had undergone neurosurgical treatment followed by adjuvant chemotherapy and radiotherapy (22 cases) or chemotherapy alone (one child under 3 years of age). The chemotherapy was performed according the SIOP protocol (before irradiation — vincristin, carboplatin, etoposide, endoxan; maintenance chemotherapy — cisplatin, lomustin, vincristin). Irradiation therapy was applied to the entire central nervous system (CNS), *i.e.* the spinal cord and brain, at the dose of 35 Gy, increasing to 54Gy when irradiating the site of the removed tumour.

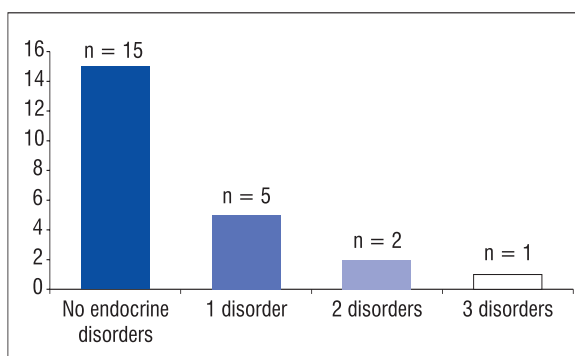
In all cases the auxological measurements and hormonal investigations were repeated after completion of the treatment, 3 months after the treatment, and every 6 months for 3 years after the treatment. Growth hormone (GH) stimulation tests were performed in patients that presented auxological symptoms of GH deficiency (a decrease of the growth velocity below — 2SD for sex and age or below the predicted final high — MPH - and delayed bone age over 2 years in comparison to the chronological age). Bone density was measured in 2 patients with GH deficiency and in 1 patient with hypogonadotropic hypogonadism. Primary hypothyroidism was defined as decreased  $fT_4$  and

$fT_3$  levels with an elevated TSH level; secondary hypothyroidism was defined as decreased  $fT_4$  and  $fT_3$  with a low TSH level. Growth velocity deceleration was recognised when a decrease of growth rate was at least 1 SD in a 6-month observation period. GH deficiency was diagnosed when the auxological criteria and serum GH secretion in the standardized growth hormone stimulation test was below 10 ng/ml. Any 2 of the following 3 stimulation tests were performed: clonidine test (a single oral dose of 150 mcg/m<sup>2</sup>, blood samples were taken before and 30, 60, 90, and 120 minutes after clonidine), glucagon test (a single intramuscular dose of 0.03 mg/kg body mass, not more than 1 mg, blood samples were taken 30 minutes before injection and 0, 60, 90, 120, 150, and 180 minutes after glucagon administration), insulin test (a single, subcutaneous dose of 0.05–0.1 IU/kg body mass, blood samples were taken before and 30, 60, 90, and 120 minutes after insulin administration). Hypogonadism was defined as a lack of breast development after 13 years of age in girls and lack of testes enlargement (volume < 4 ml) after 14 years of age in boys, as well as no progress to full sexual development in 4 years from the first signs thereof. Hypogonadotropic hypogonadism was recognized when concentrations of sex hormones and gonadotropins were below normal range. Hypergonadotropic hypogonadism was recognized when, in a patient with low concentrations of sex hormones, increased concentrations of LH and FSH were found. The hormone level analysis was performed using the following methods: TSH,  $fT_3$ ,  $fT_4$ , LH, and FSH with the LIA method (Bayer), ACTH-IRMA, Brahms, GH-IRMA, Polaton, IGF-I-IRMA, Biosearch. The reference levels for the hormones were obtained from the Department of Biochemistry in our Hospital.

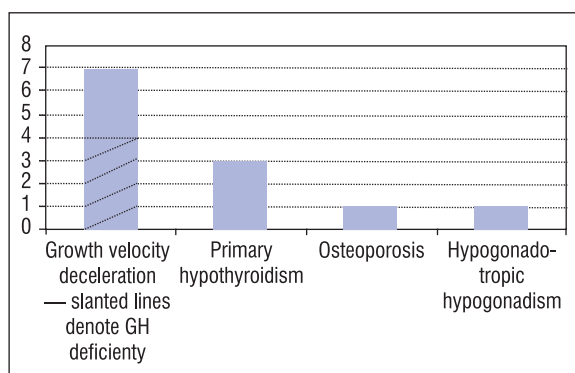
Osteoporosis was diagnosed when a decrease in bone mineral density in reference to bone age yielded a Z-score below — 2SD in densitometry (DEXA).

## Results

In the study group of 23 patients, no pre-therapy abnormalities were noted in auxometric measurements or hormone levels. In the first three years after medulloblastoma treatment, endocrine disorders were found in 8 patients (3 boys aged 6, 13, and 17 years, and 5 girls aged 9, 9 and 8/12, 10, 11 and 14 years). Five patients presented with single disorder, 2 with two abnormalities, and 1 patient manifested three disorders. Fifteen patients showed no endocrine disorders (Fig. 1). Among the patients with 2 disorders, 1 child presented with a decrease of growth rate and primary hy-



**Figure 1.** Endocrine disorders in children after medulloblastoma treatment



**Figure 2.** Number of children with particular endocrine disorders

pothyroidism, and the other with GH deficiency and osteoporosis. The patient with 3 disorders manifested growth retardation, primary hypothyroidism, and hypogonadotropic hypogonadism (Fig. 1).

The most common abnormalities included decelerated growth velocity ( $n = 7$ ), followed by primary hypothyroidism ( $n = 3$ ), hypogonadotropic hypogonadism ( $n = 1$ ), and osteoporosis ( $n = 1$ ). Of 7 children with growth velocity deceleration (3 boys, 4 girls), 4 were found to be GH-deficient. One child died prior to initiation of biosynthetic human growth hormone therapy; the remaining 3 patients continue their GH substitution therapy. Fifteen patients showed no endocrine disorders (Fig. 2).

As presented in Table 1, hypogonadotropic hypogonadism was the first complication observed after completion of the treatment (in the first 3 months post-therapy). Growth velocity deceleration was noted between 4 and 24 months following the treatment. Primary hypothyroidism was diagnosed between 7 and 36 months. None of the patients was diagnosed with secondary hypothyroidism. Osteoporosis was noted in 1 child with GH deficiency as late as almost 24 months after medulloblastoma treatment (Table 1).

**Table 1. Time of the onset of particular symptoms after completion of therapy**

Time of symptom onset after completion of therapy (in months)	0–3	4–6	7–12	13–18	19–24	25–36
Growth velocity deceleration — GH deficiency		n = 1	n = 1		n = 2	
Other causes of growth velocity deceleration		n = 2	n = 1			
Primary hypothyroidism			n = 1		n = 1	n = 1
Osteoporosis					n = 1	
Hypogonadotropic hypogonadism	n = 1					

n — number of patients manifesting a given disorder

## Discussion

The recently observed improvement in therapeutic outcome in CSN malignancies has resulted in the increasing survival of patients and has revealed the issue of late endocrine complications. Such sequelae may affect the secretion of one or more hormones and occur at various time intervals following completion of the treatment. Prior to the therapy, none of the patients from the investigated group demonstrated any endocrine abnormalities. However, after the treatment endocrine disorders were observed in 8 of the 23 children (34%). These disorders included growth deficiency, primary hypothyroidism, hypogonadotropic hypogonadism, and osteoporosis. Three patients developed more than one endocrinopathy. The prevalence of complications and their onset following completion of therapy were not dependent on age or sex of the patients.

The most common finding was growth velocity deceleration, which was seen within the 2 years after treatment in 7 of the 23 patients; this observation is in accordance with data reported by other authors [1, 2]. In the present material, in 50% of the cases the cause of this disorder was growth hormone deficiency, probably resulting from the total irradiation dose, *i.e.* 35Gy, with an increased dose of 54Gy applied to the site of the removed tumour. As it follows from reports of numerous authors, GH deficiency usually occurs when the total dose exceeds 30Gy [1], while a dose of 18–30Gy may result in GH deficiency in approximately 1/3 of patients. A dose below 18Gy [7] is believed to be safe, although a few authors suggest that GH deficiency may develop even at lower irradiation doses, well below 18Gy. In the present material, in 3 of 7 patients with growth velocity deceleration, in whom no GH deficiency was detected, growth delay might have resulted from damage to the spinal growth cartilages during spinal cord irradiation [1] and/or additional injury in the course of chemotherapy [9]. Yet, in these patients, GH deficiency developing later in life cannot be ruled

out as the cause of growth deficiency; similarly, these 2 disorders (GH deficiency and damage to the growth cartilages) cannot be excluded in patients without growth abnormalities detected within 3 years following medulloblastoma treatment completion. Such a conclusion follows from the GH deficiency observed by other authors developing as late as 25 years after treatment completion [12], and the increasing incidence of growth deficiency, which is observed in as many as 70–80% with increasing time after medulloblastoma treatment [1,2].

The second most common endocrinopathy encountered in the investigated group was primary hypothyroidism, observed in 3 of 23 patients (13%). No secondary hypothyroidism was noted, however, which may be explained by a higher sensitivity to irradiation exhibited by thyrocytes as compared to hypophyseal thyrotropes. This is confirmed by the ten times higher prevalence of primary, as compared to secondary, hypothyroidism (30–50% vs. 3–6%) observed in another group of patients following spinal cord irradiation with a dose exceeding 10Gy [17]. The onset of hypothyroidism was noted in the present group 7 months after completion of therapy at the earliest, while 2 patients demonstrated hypothyroidism within 24 months post-therapy, *i.e.* somewhat earlier than data reported by other authors (the earliest reported occurrence was 10 months after therapy, with the mean time of 41 months)[1]. It should be stressed that in investigations carried out by other authors, the majority of hypothyroidism cases manifested later than 3 years after therapy completion, even as late as 18 years [1]. The data indicate the necessity of monitoring thyroid function for at least 20 years after medulloblastoma treatment, starting in the first 6 months post-therapeutically.

Precocious puberty, delayed puberty, and no progress in puberty resulting from hypothalamic or gonadal damage (hypogonadism) are well documented complications of radio and chemotherapy in children [1, 2]. The degree of gonadal damage depends on the age at therapy initiation and the cytotoxicity of the employed chemotherapy. The testes are more sensitive

to the toxic effects of chemo and radiotherapy than are the ovaries [1]. With the chemotherapy and radiotherapy protocol employed in the investigated group, hypogonadism resulting from damage to the hypothalamus (hypogonadotropic hypogonadism) was diagnosed in one girl (4.3%) 3 months after therapy completion. Within the three-month follow-up, no gonadal damage was observed. The available literature reports the incidence of this complication in medulloblastoma patients below 15%, but it is the most frequently diagnosed complication within 3 years of the therapy [17,18]. A similar incidence rate is also reported in the case of secondary dysfunction of the hypothalamo-hypophyseal-adrenal axis [17, 24, 25]. In the presented material, not a single case of adrenal insufficiency was noted. The assessment was, however, based on baseline cortisol and ACTH values rather than post-ACTH and insulin-mediated hypoglycaemia stimulation levels, as has been suggested by some authors.

A single case of osteoporosis was observed in the presented group; the disorder developed 2 years after the completion of therapy. The complication seemed to be secondary to the GH deficiency detected in this patient. Osteoporosis may be also expected in patients with hypogonadism, especially when sex hormone substitution is delayed.

According to data from the present investigation and reports available in the literature, post-medulloblastoma treatment endocrinopathies may develop starting in the initial months after treatment and up to as late as 25 years post therapy. In view of the risk of relapse and development of complications other than those of endocrine character, there is a need for close collabora-

tion between oncologists, neurosurgeons, and endocrinologists in monitoring potential disorders. The present authors suggest the following protocol for diagnosing and monitoring endocrine disorders:

I. Prior to the initiation of treatment (chemotherapy and radiotherapy) — auxological examinations: height, weight, evaluation of growth velocity using growth charts appropriate for a given population, assessment of puberty according to Tanner's scale, as well as hormonal determinations: LH, FSH, ACTH, cortisol, TSH,  $fT_4$ ,  $fT_3$ , PRL, and IGF-1.

II. After completion of treatment: auxological and hormonal assessment as before therapy, to be repeated every 6 months up to 4 years after completion of treatment. Subsequently, every year: auxological assessment until the patient completes the process of growing and sexual maturation, and hormonal determinations throughout his/her entire life.

III. Prior to treatment and every year afterwards, imaging studies should be performed including bone age (left wrist and hand X-ray — to be repeated until the completion of growth), thyroid ultrasound, ultrasound of the minor pelvis in girls, and densitometry in patients with GH or sex hormone deficiency.

The protocol of examinations should focus on clinical symptoms of endocrine disorders:

\*determinations of gonadotropins levels and ultrasound of the minor pelvis are pointless before puberty; in post-pubertal patients, these examinations should be performed in case the patient presents with clinical pubertal disturbances,

\*\*estimation of IGF-1 is indicated in patients with decelerated growth velocity as detected by auxology.

## References

- Birch J.M., Marsden H.B.: A classification scheme for childhood cancer. *Int. J. Cancer* 1987; 40: 620–624.
- Blair V., Birch J.M.: Patterns and temporal trends in the incidence of malignant disease in children. II. Solid tumors of childhood. *Euro. J. Cancer* 1994; 30: 1498–1511.
- Packer R.J., Cogen P., Vezina G., Rorke L.B.: Medulloblastoma: clinical and biologic aspects. *Neuro-oncology* 1999; 1: 232–250.
- Jallo G. Medulloblastoma. <http://www.emedicine.com/neuro/topic624.htm>.10.01.07.
- MacDonald T. Medulloblastoma. <http://www.emedicine.com/ped/topic1396.htm> 07.01.07.
- Duffner P.K., Horowitz M.E., Krischer J.P. et al.: Postoperative chemotherapy and delayed radiation in children less than three years of age with malignant brain tumors. *NEJM* 1993; 17: 1725–1731.
- Xu W., Janss A., Packer R.J., Phillips P., Goldwein J., Moshang T. Jr.: Endocrine outcome in children with medulloblastoma treated with 18 Gy of craniospinal radiation therapy. *Neuro-oncology* 2004; 6: 113–118.
- Jakacki R.I., Feldman H., Jamison C., Boaz J.C., Leurssen T.G., Timmerman T.G.: A pilot study of pre-irradiation chemotherapy and 1800 cGy craniospinal irradiation in young children with medulloblastoma. *Int. J. Radiation. Oncology, Biology, Physics* 2004; 60: 531–536.
- Olshan J.S., Gubernick J., Packer R.J., D'Agio G.J., Goldwein J.W., Willi S.M., Moshang T. Jr.: The effects of adjuvant chemotherapy on growth in children with medulloblastoma. *Cancer* 1992; 70: 2013–2017.
- Shalet S.M., Beardwell C.G., Pearson D. et al.: The effect of varying doses of cerebral irradiation on growth hormone production in childhood. *Clin. Endocrinol.* 1976; 5: 287–290.
- Murray R.D., Darzy K.H., Gleeson H.K. et al.: GH-deficient survivors of childhood cancer: GH replacement during adult life. *JCEM* 2002; 87: 129–135.
- Heikens J., Michiels E.M., Behrendt H., Ender E., Bakier P.J., Fliers E.: Long-term neuro-endocrine sequelae after treatment for childhood medulloblastoma. *Euro. J. Cancer* 1998; 34: 1592–1597.
- Clayton P.E., Shalet S.M.: Dose dependency of time of onset of radiation-induced growth hormone deficiency. *J. Pediatr.* 1991; 118: 226–228.
- Livesey E.A., Brook C.D.G.: Gonadal dysfunction after treatment of intracranial tumors. *ADC* 1988; 63: 495–500.

15. Shalet S.M., Gibson B., Shwindell R. et al.: Effect of spinal irradiation on growth. *ADC* 1987; 62: 461–464.
16. Xu W., Janss A., Moshang T.: Adult height and adult sitting height In childhood medulloblastoma survivors. *JCEM* 2003; 88: 4677–1481.
17. Spoudeas H.A.: Disturbance of the hypothalamic-pituitary thyroid axis. In Wallace H and Green D. *Late Effects of Childhood cancer*. Arnold Hooper Headline Group, Great Britain 2004; 212–222.
18. Spoudeas H.A., Charandari E., Obrok C.G.: Hypothalamo-pituitary-adrenal axis integrity after cranial irradiation for childhood posteriori fossa tumors. *Med. & Pediatr. Oncology* 2003; 40: 224–229.
19. Corrias A., Einaudi S., Ricardi U. et al.: Thyroid diseases in patients treated during pre-puberty for medulloblastoma with different radiotherapy protocols. *J. Endocrinol. Invest.* 2001; 24: 387–392.
20. Paulino C.P.: Hypothyroidism in children with medulloblastoma: a comparison of 3600 and 2340 cGy craniospinal radiotherapy. *Int. J. Radiation. Oncology, Biology, Physics* 2002; 53: 543–547.
21. Schmiegelow M., Feldt-Rasmussen U., Rasmussen A.K., Poulsen H.S., Mülle J.: A population-based study of thyroid function after radiotherapy and chemotherapy for a childhood brain tumor. *JCEM* 2003; 88: 136–140.
22. Darzy K.H., Gleeson H.K., Shalet S.M.: Growth and neuroendocrine consequences. In Wallace H and Green D *Late Effects of Childhood cancer*. Arnold Hooper Headline Group, Great Britain 2004: 189–211.
23. Roth C., Lakonek M., Schmidberger H. et al.: Cranial irradiation induces premature activation of the gonadotropin — releasing — hormone. *Clin. Pediatr.* 2001; 213: 239–243.
24. Ahmed S.R., Shalet S.M., Campbell R.H., Deakin D.P.: Primary gonadal damage following treatment of brain tumors in childhood. *J. Pediatr.* 1983; 103: 562–565.
25. Adan L., Sainte-Rose C., Souberbielle J.C., Zucker J.M., Kalfa C., Brauner R.: Adult height after growth hormone (GH) treatment for GH deficiency due to cranial irradiation. *Med. & Pediatr. Oncology* 2000; 34: 14–19.