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## Brain metastasis from non-seminomatous germ cell tumors of the testis

### Indications for aggressive treatment

Received: 23 March 2005 / Accepted: 26 September 2005  
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**Abstract** Brain metastases from non-seminomatous germ cell tumors (NSGCTs) are rare and mainly occur in young men whose clinical condition is unimpaired. The records of 15 patients with brain metastasis from non-seminomatous germ cell tumors of the testis, who had been surgically treated between 1984 and 1998, were retrospectively reviewed. All of the patients had undergone surgery plus whole-brain radiotherapy (WBRT), and chemotherapy based on cisplatin. On admission they had a median age of 33 years and their mean Karnofsky performance scale (KPS) score was  $>70$ . Mean survival was 37.7 months. Eight patients had a survival period longer than 5 years. Five patients belonged to radiation therapy oncology group (RTOG) class I; all of them survived. There was a significant difference in survival time between patients in whom the brain metastasis was present at diagnosis (six survivors at 5 years; mean survival 53 months) and patients in whom the brain metastasis occurred during or after chemotherapy (two survivors at 5 years; mean survival 24 months) ( $P=0.04$ ). The presence of a trophoblastic component at histopathological analysis of the metastasis

negatively influenced survival at univariate analysis. Multiple brain metastasis proved to be a significant risk factor at both univariate and multivariate analysis, while a metastatic residue with a diameter less than 2 cm after surgery did not negatively affect survival in our series. Prognosis is worst in patients with multiple brain metastases, in whom brain involvement occurred during or after cisplatin-based chemotherapy. Considering that these metastases are often both radiosensitive and chemosensitive, and mainly affect young men that are in very good clinical condition, we advocate aggressive treatment with surgery plus adjuvant radiotherapy and chemotherapy. This is mandatory in patients with large metastases (diameter  $>3$  cm).

**Keywords** Brain metastases · Non-seminomatous germ cell tumor · Surgery · Prognostic factors

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### Introduction

Germ cell tumors represent the most frequent type of solid tumor in men aged between 15 years and 34 years; their incidence has doubled over the past 40 years and is approximately 2/3 per 100,000 men per year, with some geographic variance (in Denmark it is approximately 6–7 per 100,000 men) [6, 7].

Non-seminomatous germ cell tumors (NSGCTs) are more clinically aggressive than seminomas and account for about 50% of germ cell tumors. Metastases from NSGCTs are usually regional, involving the retroperitoneal lymph nodes below the renal vessels. Internal organ metastases most frequently affect the lungs and are not considered to be a negative prognostic factor as long as they are less than 5 cm and their diameter does not exceed 2 cm [6, 7].

Non-pulmonary visceral metastases are less frequent and rarely represent the only metastatic localization [6, 11].

Patients with these metastases belong to the poor risk group, according to the International Germ Cell Cancer Collaborative Group (IGCCCG), and present elevated levels of alpha-fetoprotein (AFP) and/or human chorionic gonadotrophin (hCG) in almost 80% of cases [15, 29].

Nowadays, with the aid of polychemotherapy based on cisplatin [cisplatin, vinblastine and bleomycin (PVB); bleomycin, etoposide and cisplatin (BEP); etoposide, cisplatin and ifosfamide (EPI)], approximately 80% of patients with disseminated systemic disease have a long survival time (>5 years) [4, 6, 7, 11, 23, 29, 34]. As a result of both the prolonged survival period provided by the increasing efficacy of the polychemotherapeutic protocols now available and the use of modern imaging techniques (MRI), the incidence of brain metastases is constantly on the rise in these patients [3, 5, 11, 24]. Cerebral metastases from NSGCTs of the testis are very rare in neurosurgical practice (0.5% of all cerebral metastases). They occur at the onset of the disease in approximately 2–3% of cases, whereas they are much more common (8–15%) in patients with systemic disease [2, 4, 8, 11, 29]. On the whole it is important to differentiate between patients in whom the brain metastasis occurred prior to polychemotherapy and those in whom it occurred after such treatment, since expected survival time is shorter in the latter group [11]. Of all the histotypes, pure choriocarcinoma (PC) is the one most frequently associated with brain metastases, particularly with multiple metastases localized subtentorially [2, 4, 7–9, 38]. In contrast, the presence of embryonal elements has been more frequently associated with single supratentorial cerebral lesions [2, 4, 7–9, 38].

Unfortunately, the appearance of a cerebral metastasis is an extremely unfavorable prognostic factor, since it is indicative of the most advanced stage of tumor spread (80% of these also have pulmonary metastatic lesions) [2–8, 12, 15, 23, 24, 27, 29, 34, 35, 38].

We report the results obtained in 15 patients with cerebral metastases from NSGCTs of the testis, treated by surgery, whole-brain radiotherapy (WBRT; 40–50 Gy) and chemotherapy (PVB, PEB or salvage therapy with PEI).

The indications for other therapeutic options are also discussed. In fact, radiosurgery (RS) has also proved to be an effective treatment modality for either single or multiple

brain metastases <3–3.5 cm in diameter, in patients with stable systemic disease [9, 13, 17, 18, 30, 31, 37].

Given the lack in the literature of a comparison (by means of randomized prospective trials) of the different treatment modalities available for patients with brain metastases from NSGCTs, we considered the therapeutic strategies generally adopted for brain metastasis, paying attention to the chemosensitivity and radiosensitivity of these lesions (with the exception of those which demonstrated a great number of teratomatous elements at neuropathological examination).

Furthermore, we must bear in mind that these patients are usually very young and often present a good clinical status on admission [Karnofsky performance scale (KPS) score >70] [11].

## Patients and methods

Fifteen patients with brain metastasis from non-semi-nomatous germ cell tumor were retrospectively studied. These patients were surgically treated in two different institutions (Neuromed-Pozzilli and Policlinico Umberto I-Rome) and were referred to us between 1984 and 1998 out of a catchment area of 2.5 million inhabitants.

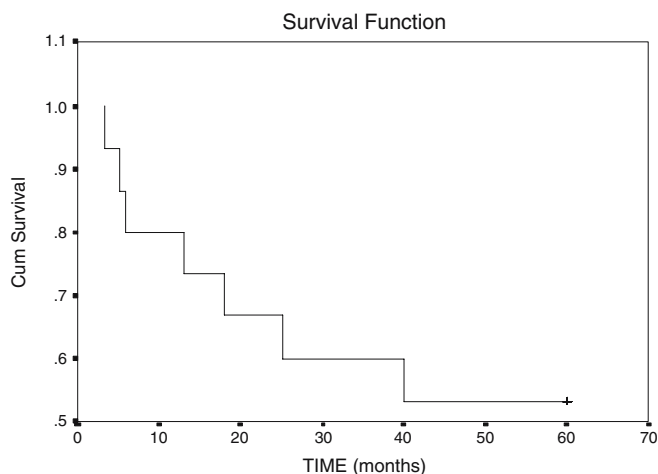
The patients were divided into two groups: group A consisted of patients in whom the brain metastasis had represented the first sign of the disease, group B patients in whom the brain metastasis had appeared during or after chemotherapy.

The study included all patients with either a single or solitary metastasis, susceptible to surgical treatment, with a KPS score >60 on admission and with a life expectancy of more than 3 months. In all these patients the systemic disease was judged to be under therapeutic control by the consultant oncologist. Patients with multiple brain metastases, for whom surgical treatment ensured a better quality of life and survival for at least 3 months, were also included.

**Table 1** Histological diagnosis of both the primary tumor, when available, and the metastasis (MTU malignant teratoma, undifferentiated, MTI malignant teratoma, intermediate)

Patient no.	Age (years)	Histopathology		Visceral site of metastases <sup>a</sup>	RTOG	KPS score
		Primitive	Metastases			
1	21	TD	TD	/	I	80
2	48	MTU	MTU	/	I	90
3	57	PC	PC	Lung (6) (4.5 cm)	III	60
4	38	MTT	PC	Lung (4) (3 cm) bone(2)	II	70
5	28	MTT	PC	Lung (3) (4 cm)	II	70
6	18	MTI	MTI	Lung (6) (2 cm)	III	60
7	47	MTU	MTT	Liver, lung (4) (4 cm)	III	60
8	29	MTU	MTT	Lung (2) (<2 cm)	II	90
9	33	MTI	MTI	/	I	90
10	36	MTT	PC	Lung (1) (2 cm)	III	60
11	27	MTT	MTT	Lung (4) (4 cm), bone	II	70
12	19	MTU	MTU	Lung (3) (5 cm)	II	70
13	35	MTI	MTI	Lung (5) (3 cm)	II	80
14	26	MTI	MTI	/	I	90
15	43	MTU	MTU	/	I	90

<sup>a</sup>Number of metastases and diameter of the largest metastasis



**Fig. 1** Graph showing overall survival data of our series (*Cum* cumulative)

On admission all patients were examined both neurologically (Glasgow coma scale) and generally, according to their KPS score. Moreover, they were also classified according to the Radiation Therapy Oncology Group (RTOG) classification.

In all cases CT and/or MRI, with and without contrast medium, was performed, as well as measurement of the serum levels of AFP and hCG. A total-body CT scan was also carried out, preoperatively and/or postoperatively, differently for each case. Histological diagnosis of both the primary tumor, when available, and the metastasis was performed according to the classification described by Collins and Pugh [9] (Table 1). Furthermore, within the group of malignant trophoblastic teratomas (MTTs), the PC

variant was deliberately distinguished, because, not only is it known to be more aggressive, but it also has a higher tendency to affect the brain [11, 35].

When multiple metastases were present we removed only the larger lesions or those considered responsible for neurological symptoms or worsening; other metastases were also removed so long as they were accessible via the same craniotomy. When possible, metastases were removed en bloc.

Resection of the metastasis was defined as macroscopically total when no residue was visible at the time of surgery, with subsequent confirmation by brain MRI or CT performed within 24 h of operation; subtotal when the residue was less than 10%; partial when the residue was less than 50%; biopsy when more than 50% of the lesion was left in situ.

In all cases, brain MRI or CT was performed within 24 h of operation; subsequently, they were repeated 1 week after operation, 1, 3 and 9 months after operation and at least every 12 months thereafter for the first 2 years after craniotomy. Furthermore, serum markers of the disease were evaluated weekly and later monthly (AFP and hCG normal levels were considered to be <15 ng/ml and <10 mIU/ml, respectively).

All patients commenced WBRT within 4 weeks of surgical treatment, with a total dose of 30 Gy to 50 Gy (in 3–6 weeks, fractioned in 20 to 30 days of treatment, single dose approximately 1.5/2 Gy), as decided by the consultant radiotherapist, for each patient; in addition to this, four cycles of polychemotherapy employing PVB or BEP were administered.

The response to radiotherapy and polychemotherapy was evaluated as follows. Complete response (CR): ab-

**Table 2** Clinical and histological features (*IH* intracranial hypertension, *FS* focal sign, *TR* total removal, *ST* subtotal removal, *BR* brain recurrence, *SD* systemic disease)

Patient no.	No. (size) of brain metastases	Site	Clinical onset	Surgery	No. (size) of residual metastases	Brain recurrence	Response to treatment	Survival time	Cause of death
1	1 (4 cm)	Temporal	IH	TR	0	No	Complete	>60 months	Alive
2	1 (3 cm)	Frontal	FS	TR	0	No	Complete	>60 months	Alive
3	3 (4.5; 2.5; 1.5 cm)	Cerebellar	Bleeding	TR	2 (2.5 e 1.5 cm)	YES	Absent	3.3 months <sup>a</sup>	BR
4	2 (5; 2.5 cm)	Parietal	Bleeding	TR	0	No	Absent	6 months <sup>a</sup>	SD
5	2 (4.5; 2 cm)	Cerebellar	IH	TR	1 (2 cm)	YES	Absent	13 months <sup>a</sup>	BR
6	2 (3; 1 cm)	Temporal parietal	Seizures	TR	0	No	Partial	25 months <sup>a</sup>	SD
7	3 (5; 3; 2 cm)	Frontoparietal	Bleeding	TR e ST	1 (3 cm)	YES	Absent	5 months <sup>a</sup>	SD
8	1 (3.5 cm)	Frontoparietal	Seizures	TR	0	No	Partial	40 months <sup>a</sup>	SD
9	1 (2 cm)	Temporal	Seizures	TR	0	No	Complete	>60 months	Alive
10	2 (4.5; 1 cm)	Parietal occipital	Bleeding	TR	1 (1 cm)	No	Complete	>60 months	Alive
11	2 (4; 1 cm)	Cerebellar	IH	TR	1 (1 cm)	No	Partial	18 months <sup>a</sup>	SD
12	1 (3 cm)	Parietal	FS	<b>TR</b>	0	No	Complete	>60 months	Alive
13	1 (2.5 cm)	Temporal	Seizures	TR	0	No	Complete	>60 months	Alive
14	1 (2 cm)	Parietal	Seizures	TR	0	No	Complete	>60 months	Alive
15	2 (4.5 cm; 2 cm)	Frontal	FS	TR	1 (2 cm)	No	Complete	60 months	Alive

<sup>a</sup>Death

sence of intra-cerebral and extra-cerebral lesions, normalization of serum tumor markers; partial response (PR): normalization of serum tumor markers and reduction of the volume of the metastases not treated by surgery. When there was local recurrence or new extra-cerebral metastatic lesions or other cerebral repetitions, the response to radiotherapy and chemotherapy was considered to be nil.

Patients with brain metastases that had occurred after commencement of chemotherapy were submitted to salvage therapy with ifosfamide, mesna, cisplatin and etoposide.

The survival curve obtained from our patients was evaluated by the Kaplan–Meier method, and the influence on survival of the different covariates was evaluated by the log-rank method [18].

The variables tested by univariate analysis were: KPS score on admission (KPS >70 vs KPS <70), histopathology of the brain metastasis and the primary lesion (MTT and PC vs the other histotypes), presence of non-pulmonary metastases of the internal organs (liver and bones), presence of multiple cerebral metastatic lesions and the presence of residues of cerebral metastatic lesions with a diameter >2 cm.

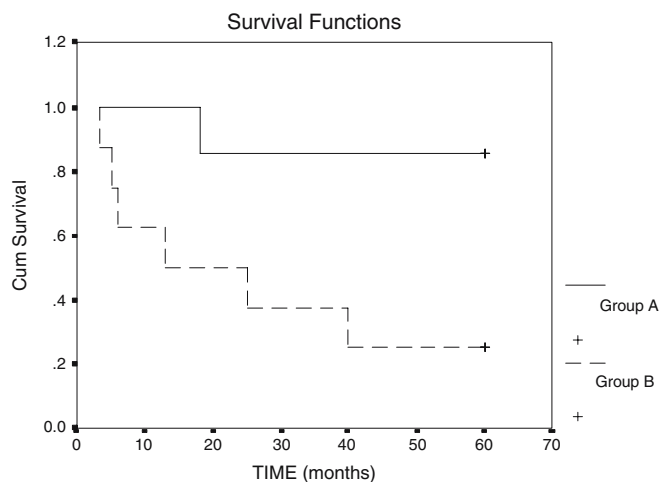
## Results

Overall survival of our patients is illustrated by the Kaplan–Meier curve (Fig. 1).

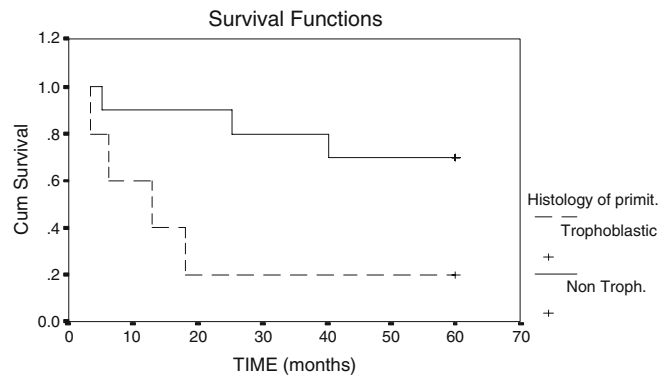
Their clinical and histological features are summarized in Tables 1 and 2.

Age ranged from 18 years to 57 years. Mean age and median age of our patients was 33 years. Average survival time is 37.7 months; 5-year survival rate is 53% (eight patients).

All the surgically treated metastases were removed en bloc, (“internal no touch technique”), but one case of multiple metastasis was operated on via the same craniot-



**Fig. 2** Graph showing the difference in survival times between patients who presented metastases before (group A) and after (group B) chemotherapy. The difference in survival time was statistically significant ( $P=0.04$ ). (Cum cumulative)

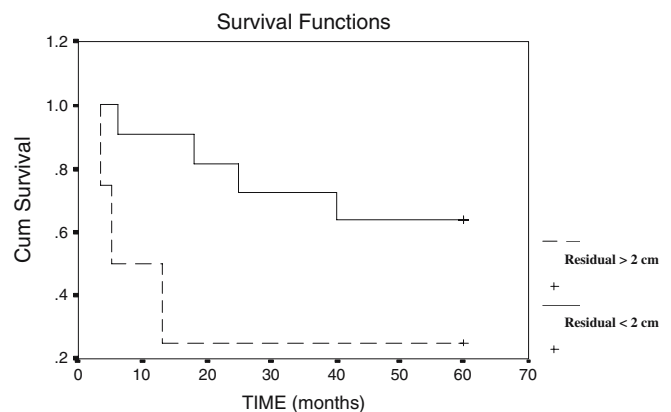


**Fig. 3** Graph showing the effect of primitive histopathology on survival. The group of patients affected by primitive cancer with trophoblastic elements (PC or MTT) was compared with the group affected by different histopathologies. (Cum cumulative)

omy (emergency operation) in which postoperative MRI evidenced subtotal removal of the hemorrhagic lesion. In the other six patients with multiple metastases, we removed only the largest and symptomatic lesions. Of these patients, three had local recurrences that proved fatal (patients 3, 5 and 7). Four patients, all affected by multiple metastatic lesions, were operated on as emergencies, because of bleeding of the lesion; one of these patients (patient no. 9) was a long-term survivor (>60 months).

Radiological follow-up consisted of CT and MRI in five patients and ten patients, respectively. Among the first five, two patients were affected by multiple metastases, of which only the largest lesion was removed. Removal of metastases in these cases was evaluated intraoperatively (the metastases were all removed en bloc) and subsequently confirmed by CT with contrast medium.

Seven patients were classed as group A, eight as group B. Six of the eight patients (75%) of group B died, whereas only one patient (15%) in group A survived for fewer than 5 years. The difference in survival times between the two groups (mean 54 months in A, mean 26 months in B) was found to be significant at statistical analysis ( $P<0.05$ ) (Fig. 2). Five patients belonged to RTOG class I; all of them survived. Six patients were class II, four class III. In five



**Fig. 4** Graph showing the effects of residual brain metastasis size on survival. The presence of a residual with a diameter  $\geq 2$  cm negatively affected survival. (Cum cumulative)

cases the histology of the metastasis differed from that of the primary lesion (cases 4, 5, 7, 8 and 9).

The presence of choriocarcinomatous elements (MTT or PC) within the cerebral metastasis was found to be an unfavorable prognostic factor ( $P<0.05$ ) (Fig. 3) at univariate analysis. Other factors that negatively influenced survival were KPS score  $<70$  ( $P<0.01$ ), multiple cerebral metastases ( $P<0.01$ ) and residues of metastases after surgery that were larger than 2 cm in diameter ( $P<0.01$ ) (Fig. 4). There were no significant complications related to surgical treatment, and those that occurred all cleared up without sequelae.

The complications of WBRT consisted of mild dementia in one patient (total dose of radiation 40 Gy; single fraction 2 Gy).

In two patients, polychemotherapy (salvage therapy with ifosfamide) had to be interrupted due to the onset of severe platelet deficiency and granulocytopenia; in both patients (patients 3 and 7) progression of the disease was very rapid.

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## Discussion

Until 25 years ago, the prognosis of patients with brain metastases from NSGCTs was dismal, and the possibility of cure extremely unlikely (mean overall survival was approximately 6–7 months) [26–28, 35]. The introduction of polychemotherapy protocols based on cisplatin and intrathecal administration of chemotherapeutic drugs brought about a significant improvement [12, 30]. The initial treatment did not include radiotherapy or surgery as alternative or complementary forms of treatment to the polychemotherapeutic protocol proposed [30]. This protocol underestimated the importance of the frequent occurrence of bleeding in metastases from NSGCTs submitted to chemotherapy alone; the hemorrhage was the result of tumoral lysis, which, when localized in the brain, may lead to severe damage and even death [30].

Although the NSGCT has a certain amount of radiosensitivity, it is less than that of the seminoma [6]. Nevertheless, tumors with consistent teratomatous elements are often resistant to both chemotherapy and radiotherapy [4].

Radiotherapy has only been demonstrated to have a curative effect in small tumors; in fact, according to Peckham and Barrett, the success rates of radiotherapy for eliminating metastases from NSGCTs are: 100% for metastases less than 1 cm in diameter, 75% for those between 1 cm and 2 cm, 31% for those over 2 cm and 0% for those over 6 cm [27]. Thus, subsequently, WBRT was combined with chemotherapy [1, 14, 19, 21, 26]. Nowadays, as demonstrated by the multicentric study by Fossa et al., the best treatment available for brain metastases from NSGCTs is surgery plus chemotherapy and WBRT [11]. In fact, in this series, surgery was demonstrated to be a positive prognostic factor by both univariate and multivariate analysis, as well as in the case series described by Bokemeyer et al., in which patients submitted to surgery of the metastasis survived longer than those treated by chemotherapy and radiotherapy alone (2 years survival rates were 75% and 25%, respectively) [4, 11].

In a recent series reported by Lutterbach et al., all long-term survivors had been submitted to surgery as well [22]. Consequently, those authors also advocate surgery plus postoperative WBRT for patients with advanced extra-cerebral disease and/or isolated cerebral relapse [22].

In the past, the belief that metastases from NSGCTs of the testis should not be surgically treated was founded on the fact that they are often multiple (in particular those from MTT or from pure choriocarcinoma) and, therefore, like all other multiple metastases, should not have been operated on [3].

According to Bindal et al., surgical treatment is also indicated for patients with multiple metastatic brain lesions with a life expectancy of more than 3 months, so long as the lesions are all surgically accessible (even when this requires more than one craniotomy), as well as for severely symptomatic or life-threatening lesions [3].

Moreover, Iwadate et al., suggested that, even when resection of all the brain metastases is not feasible, the largest lesions should be surgically removed; this permits mainly a better quality of life and survival comparable to that observed in patients with a single, surgically treated, brain metastasis, and, in any event, longer than those obtainable using conservative methods alone (corticosteroids and WBRT) [16, 33]. In fact, in Iwadate's series, so long as the residual metastases do not exceed 2 cm in diameter, survival times of patients affected by single and multiple brain metastases from several different malignancies are not significantly different (within the group of the same primitive malignancy) at statistical analysis [16]. This statement has even more relevance, particularly in lesions as chemosensitive and radiosensitive as cerebral metastases from NSGCTs of the testis, in which the size of the residual metastases can impair the results of adjuvant treatments such as radiotherapy and chemotherapy.

In fact, nowadays, in virtue of the radiosensitivity of NSGCTs and the encouraging results obtained with polychemotherapy (BEP and salvage therapy with ifosfamide), it is even possible to cure metastases less than 3 cm in diameter not surgically excised [23]. In our patients, the difference in survival between those with a residue  $>2$  cm and those with a residue  $<2$  cm was found to be significant at univariate analyses (Fig. 4).

Over the past 10 years, far more importance has been given to radiosurgery (with or without subsequent WBRT) for the management of either single or multiple brain metastases [6, 10, 14, 19, 25, 26, 28, 32]. In fact, in selected cases (multiple small brain metastases up to three in number and with a diameter not exceeding 3 cm) it provides results comparable to those obtained with surgery plus WBRT, with the added advantage of being able to treat surgically inaccessible lesions [14, 28].

Recently, Pollock et al. reported excellent survival data in properly selected patients with multiple brain metastases from several different malignancies, treated aggressively with either stereotactic radiosurgery (SRS) or multiple craniotomies and tumor resection, or a combination of both [28]. Such an aggressive therapeutic strategy is particularly indicated for patients possessing the following positive

factors for survival: age <65 years, radiosensitive tumors and a good clinical status (KPS score >70), such as most of the patients affected by brain metastasis from NSGCTs, (in our series median age was 33 years and mean Karnofsky score was above 70) [28]. For these reasons management of brain metastases from NSGCTs should be very aggressive, with surgical resection of all the larger, accessible cerebral metastases, even when it is impossible to remove the smallest lesions, followed by postoperative WBRT and cisplatin-based polychemotherapy [23]. The option of combining craniotomies and radiosurgery as suggested by Pollock et al. should also be considered [28].

On the other hand, in cases of surgically inaccessible metastases with a diameter <3–3.5 cm, radiosurgery with or without WBRT should be the treatment of choice [6, 10, 14, 19, 25, 26, 28, 32, 34].

Of course, side effects and complications of such an aggressive strategy may be very relevant, especially in young patients, and therefore deserve some consideration.

The effectiveness of postoperative WBRT after surgery or radiosurgery, in the treatment of brain metastases in general, is controversial [1, 10, 16, 26]. Some authors have pointed out the risks of sequelae from postoperative WBRT, particularly dementia, (which occurred in one patient in our series, who was affected by multiple brain metastases and underwent a total amount of radiation =40 Gy), which is particularly devastating in a young person [10].

The randomized trial reported by Patchell et al., showed that WBRT is mainly effective in reducing brain recurrence while it does not seem to prolong survival time [24, 26]. According to this study patients treated with postoperative WBRT mainly die as a result of their systemic disease, while their residual survival is improved by a better control of the disease in the brain, both at the site of surgery and at any distant brain locations [26]. This is a remarkable result, particularly in metastases evidenced at the onset of very chemosensitive and curable tumors such as NSGCT of the testis. In fact, WBRT helps in preventing brain recurrence of the metastasis, while cisplatin-based polychemotherapy is more effective in controlling systemic disease.

Nowadays, the concept of the brain as an inaccessible sanctuary for metastases is no longer acceptable, because, in patients with cerebral metastases, it is possible to permeate the blood–brain barrier by means of high concentrations of cisplatin, etoposide and bleomycin or ifosfamide [11, 12, 22, 27, 30, 31, 33, 36]. The real problem, besides the blood–brain barrier, is that, in some cases, the tumor does not respond well to chemotherapy. In fact, it is necessary to make a distinction between patients with metastases that appeared after chemotherapy and those in whom the cerebral metastasis was the first sign of the disease, or appeared before commencement of chemotherapy [11].

The difference between the 2 groups, in terms of both 2-year survival rates and cure (>5 years), is considerable: survival was shorter in patients with metastases that appeared after induction of chemotherapy of the primary tumor, in both the cases reported in the literature and those treated personally [3, 5] (Fig. 2).

Chemotherapy may select the most aggressive, drug-resistant cellular clones, and it is no coincidence that cerebral metastases sometimes present a different histotype from the primary lesion. In particular, cerebral metastases from primary tumors with an undifferentiated component (malignant undifferentiated teratoma) or a mixed component with areas of cytotrophoblastic cells (malignant trophoblastic teratoma) previously treated by polychemotherapy, frequently present the histological features of PC and present more aggressive behavior, as confirmed by the survival rates both in our cases and in the literature [2]. In contrast, metastases from PCs almost always seem to maintain the same histology as the primary tumor. Moreover, the presence of a choriocarcinomatous histotype represents a negative prognostic variable, as confirmed by our cases too ( $P<0.01$ ) (Fig. 3).

As far as the fairly positive outcome in terms of survival observed in our patients is concerned, we must bear in mind that such results could have been affected by surgical treatment, which has already been identified as a positive prognostic factor and undoubtedly represents a selection bias [2, 3, 5, 7–9, 11, 13, 15, 16, 20–26, 29–31, 33–38].

On the other hand, we must take into account the fact that this retrospective study also comprised patients submitted to emergency surgery because their life was at risk and with a poor estimated chance of survival. Moreover, most of these patients had multiple metastases.

The tendency of these metastases to bleed makes conservative treatment inadvisable in surgically accessible lesions (owing to tumoral lysis induced by chemotherapy, as previously reported) and was the reason why many patients affected by multiple cerebral lesions were in critical condition [20].

In the retrospective multicentric study reported by Fossa et al, in which data were collected for 12 years from nine different institutions, surgery was almost never the first-line therapy for this metastasis. In fact, it was offered to only those patients whose clinical condition was poor, such as those suffering from highly symptomatic or life-threatening lesions or in whom the brain was involved by the tumor after chemotherapy [11, 12].

In spite of the high risks in this group of patients, surgery offered better survival results than other types of treatment. In our series, all the patients submitted to emergency operation, in whom it was not possible to remove all the metastases, survived for more than 3 months, and one was disease-free at 5 years. Another patient (patient 15), who already had lung and multiple brain metastases at onset of the disease, underwent surgical removal of the symptomatic cerebral metastasis and presented an excellent response to WBRT and cisplatin-based polychemotherapy: the disease completely disappeared and survival time was >60 months.

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## Conclusion

NSGCT of the testis is a tumor that may present a very good response to chemotherapy and radiotherapy. It mainly

affects young men who are often in good clinical condition on admission.

Prognosis for these metastases is fair, and, in some cases, cure is possible, even if they are multiple at presentation; hence the need for an aggressive therapeutic strategy.

The most suitable treatment in patients with cerebral metastases from NSGCTs is surgical removal of the lesion followed by chemotherapy with BEP, PVB or with ifosfamide salvage therapy, plus WBRT.

Considering their high tendency to bleed, it is not advisable to start chemotherapy of surgically excisable metastases.

Since patients with pulmonary metastases from NSGCTs have a risk of developing cerebral metastases, periodic MRI investigations are advisable.

Multiple metastases should be treated surgically, even if it is not possible to resect them all, as long as the size of the residual lesions does not exceed 2–2.5 cm in diameter.

Otherwise, in cases of inaccessible brain metastases, radiosurgery must be considered.

In our series, negative prognostic factors proved to be:

1. Onset of the metastasis after commencement of chemotherapy (Fig. 2)
2. Presence of a cytotrophoblastic component in the metastasis (MTT or pure choriocarcinoma) (Fig. 3)
3. KPS score <70
4. Presence of multiple metastases or residues more than 2 cm in diameter not accessible to surgical resection (Fig. 4)
5. Only covariates at point (1) and (4) were also significant at multivariate analysis

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