EUROPEAN JOURNAL OF CANCER 45 (2009) 1728–1732

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Short Communication

Local control of the primary tumour in metastatic neuroblastoma

Iyad Sultan[a,*], *Khalil Ghandour*[b], *Usama Al-Jumaily*[a], *Sameh Hashem*[c], *Carlos Rodriguez-Galindo*[d]

[a]*Department of Pediatric Oncology, King Hussein Cancer Centre (KHCC), Queen Rania Street, P.O. Box 1269, Al-Jubeiha, Amman 11941, Jordan*
[b]*Department of Surgery, King Hussein Cancer Centre (KHCC), Amman, Jordan*
[c]*Department of Radiation Oncology, King Hussein Cancer Centre (KHCC), Amman, Jordan*
[d]*Department of Oncology, St. Jude Children's Research Hospital, Memphis, TN, USA*

ARTICLE INFO

Article history:
Received 29 March 2009
Accepted 20 April 2009
Available online 15 May 2009

Keywords:
High-risk neuroblastoma
Radiotherapy
Complete resection
Tumour size
SEER

ABSTRACT

The previous studies have stressed on the importance of loco-regional control in the management of high-risk neuroblastoma. We searched the Surveillance, Epidemiology and End-Results (SEER) database for patients older than 2 years with metastatic neuroblastoma who were diagnosed from 1998 to 2005. We identified 291 patients (mean age, 4.35 years). The 5-year survival estimate was 53.2% ± 6.4% for patients who had complete resection of their primary tumours ($n = 116$) and 35.7% ± 4.7% for patients who did not have complete resection ($p = 0.003$). External-beam radiotherapy did not affect survival ($p = 0.79$); this finding has to be taken with caution due to the study limitations.

1. Introduction

Approximately 650 children receive a diagnosis of neuroblastoma annually in the United States (US),[1] and more than half of them have high-risk disease.[2] The three main elements of therapy for high-risk neuroblastoma (HRNB) are intensive systemic chemotherapy to control metastatic disease and facilitate the resection of primary tumour, surgical resection and radiotherapy for loco-regional control, and agents directed against minimal residual disease.[3] Despite this intensive approach, a large proportion of patients succumb to their disease.[4,5]

Loco-regional relapse is a significant problem and it typically heralds systemic recurrence.[6] Surgery and radiotherapy are the cornerstones of loco-regional control, but their exact roles are unclear. Attempting to analyse the impact of these modalities in the context of modern intensive treatments for HRNB, we conducted a study of patients diagnosed in the most recent era and registered in the Surveillance, Epidemiology and End-Results (SEER) open-access database.

2. Patients and Methods

Patient data were obtained from the SEER 17 registries.[7] We searched for individuals with a diagnosis of neuroblastoma

* *Corresponding author:* Tel.: +962 6 5300 460; fax: +962 6 534 2567.
E-mail address: isultan@khcc.jo (I. Sultan).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2009.04.021

or ganglioneuroblastoma according to the International Classification of Childhood Cancer, third edition (ICCC-3). The selection was narrowed to patients diagnosed between January 1998 and December 2005 who were 2–18 years old and had 'distant stage' disease, defined by the SEER staging system as spread of tumour by direct extension, discontinuous metastasis or lymphatic dissemination to sites distant from the primary tumour.

After 1998, the SEER programme introduced a new coding system for surgeries (http://seer.cancer.gov/manuals/AppendC.pdf); we used this system to encode surgeries on the basis of primary site. The 'no complete resection' category (all patients who did not undergo complete resection) included patients who underwent debulking, excisional biopsy, local tumour excision, surgery not otherwise specified (NOS), partial resection, or no cancer-directed surgery at the primary site. The resulting matrix from SEER*Stat was transferred to MedCalc for Windows, version 9.6.4.0 (MedCalc Software, Mariakerke, Belgium) to perform statistical calculations and generate survival curves. Survival estimates were calculated by the Kaplan–Meier method, with all-cause mortality as an endpoint.

3. Results

We identified 1215 patients with neuroblastoma in the SEER 17 database; of those, 291 met our search criteria (metastatic disease and age > 2 years) and had histologic confirmation of the disease. The mean age of this group was 4.35 years ± 2.85 - years (SD) and 41% were females. The mean follow-up period was 2.36 years±1.8 years (SD). Table 1 shows a comparison of the characteristics of patients who did ($n = 116$) and who did not ($n = 175$) undergo complete resection. The distribution of primary tumour sites differed significantly ($p < 0.0001$, χ^2 test): 89% of completely resected tumours arose from the adrenal gland versus 61% of tumours that did not have complete resection. The maximum dimension of the primary tumours was available for approximately two-thirds of the patients ($n = 185$; 64%); mean tumour size did not differ according to completeness of resection ($p = 0.49$). The use of radiotherapy differed significantly between patients who underwent complete resection (58%) versus patients who did not (41%; $p = 0.007$).

The estimated 5-year overall survival for the whole group ($n = 291$) was 42.2% ± 3.9% (SE), and median survival time

Table 1 – Patient characteristics, loco-regional control modalities and outcome.

Variable	All		Complete resection		No complete resection		p
	n	(%)	n	(%)	n	(%)	
Total	291		116		175		
Age							
Mean (years)	4.35		4.03		4.57		0.11
SD	2.85		2.01		1.62		
sex							
Female	120	(41.2)	50	(43.1)	70	(40.0)	0.69
Male	171	(58.8)	66	(56.9)	105	(60.0)	
Histology							
Neuroblastoma	267	(91.8)	103	(88.8)	164	(93.7)	0.11
Ganglioneuroblastoma	24	(8.2)	13	(11.2)	11	(6.3)	
Site of primary tumour							
Adrenal gland	209	(71.8)	103	(88.8)	106	(60.6)	<0.0001
Retroperitoneal	29	(10.0)	9	(7.8)	20	(11.4)	
Kidney	3	(1.0)	2	(1.7)	1	(0.6)	
Mediastinum	3	(1.0)	1	(0.9)	2	(1.1)	
Others	47	(16.2)	1	(0.9)	46	(26.3)	
Size (n = 185)							
Mean (mm)	87.7		85.1		89.9		0.49
SD	47.9		47.4		48.6		
Radiation							
EBRT[a]	139	(47.8)	67	(57.8)	72	(41.1)	0.0071
None	139	(47.8)	44	(37.9)	95	(54.3)	
Others	13	(4.5)	4	(3.4)	9	(5.1)	
Follow up							
Mean (years)	2.36		2.58		2.22		0.11
SD	1.8		2.01		1.62		
Status							
Alive	174	(59.8)	82	(70.7)	92	(52.6)	0.003
Dead	117	(40.2)	34	(29.3)	83	(47.4)	

Chi-square test (χ^2) was used to compare categorical variables and Welch test was used compare numeric variables.
a External-beam radiotherapy.

was 3.17 years (Fig. 1A). Survival was not affected by age, sex, tumour histology or site of primary tumour. The extent of surgery was significantly associated with survival. The 5-year survival estimate was 53.2% ± 6.4% for patients who underwent complete resection, compared to 35.7% ± 4.7% for patients who did not ($p = 0.003$; Fig. 1B). When we excluded patients who had no surgery or whose records indicated surgery NOS ($n = 99$), patients who underwent complete resection retained a survival advantage ($p = 0.040$). On the other hand, irradiation of the primary site did not influence survival ($p = 0.79$; Fig. 1C). We also analysed the impact of tumour size by studying different size categories. Interestingly, we observed a substantial survival advantage for patients whose tumours were ⩽45 mm in maximum dimension ($p = 0.016$; Fig. 1D). However, these smaller tumours were not significantly more likely to be completely resected; 56% of tumours ⩽45 mm and 44% of larger tumours were completely resected ($p = 0.27$).

Of the 116 complete resections, 75 were total resections and 41 were radical surgery with en bloc removal of an involved organ. Survival was similar in these two groups (5-year survival, 52% ± 13% versus 53% ± 7.6%, respectively; $p = 0.76$). Radiotherapy was administered to more than half of these patients (58%), with no significant impact on survival ($p = 0.45$).

The 175 patients who did not undergo complete resection of the primary tumour underwent partial resection ($n = 36$), local tumour excision or ablation ($n = 19$), debulking ($n = 12$), excisional biopsy ($n = 9$), surgery NOS ($n = 5$) or no cancer-directed surgery at the primary site ($n = 94$). Survival was similar among these groups of patients ($p = 0.35$).

4. Discussion

We searched the SEER 17 database for patients with HRNB diagnosed between 1998 and 2005. Because biological data and exact age in months were not available, we searched for children with metastatic disease who were older than 2 years and who met the accepted criteria for high-risk disease.[8] The studied group represented less than a quarter of all patients diagnosed with neuroblastoma/ganglioneuroblastoma in the same period. Our selection missed important groups of HRNB patients, e.g. tumours with *MYCN* amplification that are diagnosed at younger age or not presenting with distant spread. In the studied population, we confirmed that 5-year survival was consistent with the data reported in the recent era[9] to establish that the patients had been treated according to contemporary protocols.

In HRNB, the primary tumour often invades adjacent major vessels and vital structures, making surgical resection difficult.[10] However, complete resection significantly improves the odds of survival in the context of effective multimodality therapy.[11–14] For example, La Quaglia et al. reported that the survival rate was 50% in 103 patients who underwent gross total resection but only 11% in other patients ($n = 38$; $p < 0.01$).[15] On the other hand, German studies found that complete resection was not advantageous in the recent trials (NB90/95 and NB97) based on intensified chemotherapy, including consolidation with autologous hematopoietic stem cell transplantation (AHSCT) and long-term maintenance chemotherapy.[16] However, like other trials in the early

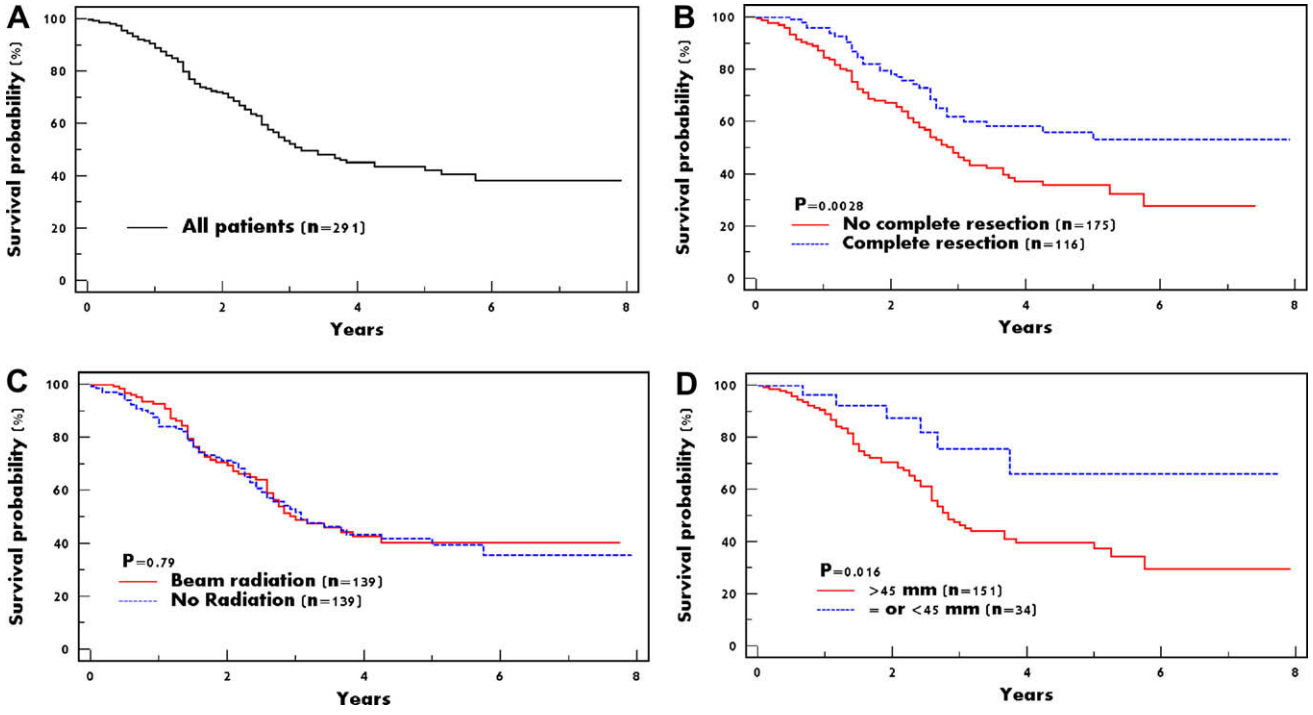

Fig. 1 – Kaplan–Meier survival curves of (A) patients older than 2 years at diagnosis of metastatic neuroblastoma (1998 through 2005) and registered in the SEER database, (B) patients with metastatic neuroblastoma who underwent complete resection versus those who did not undergo complete resection; (C) patients with metastatic neuroblastoma who received external-beam radiotherapy versus those who did not; (D) patients with metastatic neuroblastoma who had a primary tumour maximum diameter > 45 mm versus those with smaller tumours.

1990s, the aforementioned trials did not incorporate *cis*-retinoic acid, which impacts local and systemic control of HRNB.[6]

In many cases, radical surgery is necessary to completely resect a tumour, including the rare need for nephrectomy. In our study, 14% of the patients (41/291) underwent radical surgery, which we classified as complete resection. Our decision was based on the assumption that surgeons usually perform radical surgery only when complete resection is achievable.[17] Although this assumption has its limitations, the outcome of patients who underwent radical surgery was similar to those listed in the SEER database as having had total resection of the primary tumour. The details of the extent of radical resection are not listed in SEER, but the reported nephrectomy rates in the literature range from 10% to 25%,[15,17] comparable to the frequency of radical surgery in our study.

Although loco-regional radiotherapy was omitted from initial therapy for low-risk neuroblastoma after some debate,[18] this modality is included in most current protocols for high-risk neuroblastoma.[11] The CCG-3891 study randomised 539 patients to receive consolidation with ASTHD versus further chemotherapy, followed by another randomisation to test the role of *cis*-retinoic acid.[4] The used myeloablative regimen included total body irradiation (TBI), thus patients receiving ASTHD had higher total dose of radiation delivered to the tumour bed. Local failure was significantly decreased in the ASTHD arm (22% ± 12% versus 52% ± 8% in the chemotherapy arm, $p = 0.022$).[6] The radiotherapy doses used were on the lower side (10–20 Gy). These doses may be inadequate for some patients, such as those with unfavourable biological factors and bulky residual disease who may require higher doses of radiation.[19,20]

Our study showed no survival benefit for patients who received radiotherapy as part of their initial treatment, including those who did not undergo complete resection of their primary tumours. The absence of details of radiotherapy, including doses, timing and volume, from the SEER database limits the scope of our findings.

Another limitation of our study is the absence of information about disease status at the time of local control therapy; therefore, our analysis may have been biased by the underrepresentation of patients whose disease progressed during chemotherapy. The impact of surgery was maintained even when patients who underwent no surgery or whose surgery was NOS were excluded; this approach focused our analysis only on patients who underwent surgical resection as part of primary therapy, which is usually done with curative intent. Further, radiotherapy showed no benefit either in patients who had complete resection or in those who had other types of surgeries.

The findings of our study must be interpreted cautiously because of the mentioned limitations. Despite these limitations, the role of complete surgical resection as shown in our study is supported in the literature. Radiotherapy benefit, potential indications and needed doses require further evaluation.

Conflict of interest statement

None declared.

Acknowledgements

The authors like to acknowledge Ms. Sharon Naron from St. Jude Children's Research Hospital for reviewing and editing this manuscript. The authors also acknowledge American Lebanese Syrian Associated Charities (ALSAC) and the King Hussein Cancer Foundation (KHCF) for their support to St. Jude Children's Research Hospital and King Hussein Cancer Centre, respectively.

Financial Support: None.

REFERENCES

1. Goodman MT, Gurney JG, Smith MA, Olshan AF. Sympathetic nervous system tumors. In: *Cancer incidence and survival among children and adolescents: United States SEER Program 1975–1995*. Bethesda, MD: NIH Pub. No. 99-4649; 1999. p. 65–72.
2. Mora J, Gerald WL, Qin J, Cheung NK. Evolving significance of prognostic markers associated with treatment improvement in patients with stage 4 neuroblastoma. *Cancer* 2002;**94**(10):2756–65.
3. Reynolds CP. [p]Detection and treatment of minimal residual disease in high-risk neuroblastoma. *Pediatr Transplant* 2004;**8**(Suppl 5):56–66.
4. Matthay KK, Villablanca JG, Seeger RC, Stram DO, Harris RE, Ramsay NK, et al. Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy, autologous bone marrow transplantation, and 13-*cis*-retinoic acid. Children's Cancer Group. *New Engl J Med* 1999;**341**(16):1165–73.
5. Kletzel M, Katzenstein HM, Haut PR, et al. Treatment of high-risk neuroblastoma with triple-tandem high-dose therapy and stem-cell rescue: results of the Chicago Pilot II Study. *J Clin Oncol* 2002;**20**(9):2284–92.
6. Haas-Kogan DA, Swift PS, Selch M, et al. Impact of radiotherapy for high-risk neuroblastoma: a Children's Cancer Group study. *Int J Radiat Oncol Biol Phys* 2003;**56**(1):28–39.
7. Surveillance, Epidemiology and End Results (SEER) Program <www.seer.cancer.gov>. SEER*Stat Database: Incidence – SEER 17 Regs Limited-Use + Hurricane Katrina Impacted Louisiana Cases, Nov 2007 Sub (1973–2005 varying) – Linked To County Attributes – Total US, 1969–2005 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2008, based on the November 2007 submission.
8. Schmidt ML, Lal A, Seeger RC, Maris JM, Shimada H, O'Leary M, et al. [p]Favorable prognosis for patients 12 to 18 months of age with stage 4 nonamplified MYCN neuroblastoma: a Children's Cancer Group Study. *J Clin Oncol* 2005;**23**(27):6474–80.
9. Kushner BH, Cheung NK. Neuroblastoma – from genetic profiles to clinical challenge. *New Engl J Med* 2005;**353**(21):2215–7.
10. Castel V, Tovar JA, Costa E, et al. The role of surgery in stage IV neuroblastoma. *J Pediatr Surg* 2002;**37**(11):1574–8.
11. von Allmen D, Grupp S, Diller L, et al. Aggressive surgical therapy and radiotherapy for patients with high-risk neuroblastoma treated with rapid sequence tandem transplant. *J Pediatr Surg* 2005;**40**(6):936–41. discussion 941.
12. Wolden SL, Gollamudi SV, Kushner BH, et al. Local control with multimodality therapy for stage 4 neuroblastoma. *Int J Radiat Oncol Biol Phys* 2000;**46**(4):969–74.
13. Koh CC, Sheu JC, Liang DC, Chen SH, Liu HC. Complete surgical resection plus chemotherapy prolongs survival in

children with stage 4 neuroblastoma. *Pediatr Surg Int* 2005;**21**(2):69–72.
14. Adkins ES, Sawin R, Gerbing RB, London WB, Matthay KK, Haase GM. Efficacy of complete resection for high-risk neuroblastoma: a Children's Cancer Group study. *J Pediatr Surg* 2004;**39**(6):931–6.
15. La Quaglia MP, Kushner BH, Su W, et al. The impact of gross total resection on local control and survival in high-risk neuroblastoma. *J Pediatr Surg* 2004;**39**(3):412–7. discussion 412–7.
16. von Schweinitz D, Hero B, Berthold F. The impact of surgical radicality on outcome in childhood neuroblastoma. *Eur J Pediatr Surg* 2002;**12**(6):402–9.
17. Shamberger RC, Smith EI, Joshi VV, et al. The risk of nephrectomy during local control in abdominal neuroblastoma. *J Pediatr Surg* 1998;**33**(2):161–4.
18. Cheung NK, Kushner BH. Risks outweighed benefits from local radiation for non-stage 4 neuroblastoma. *Int J Radiat Oncol Biol Phys* 2002;**54**(5):1575. author reply 1575.
19. Kushner BH, Wolden S, LaQuaglia MP, et al. Hyperfractionated low-dose radiotherapy for high-risk neuroblastoma after intensive chemotherapy and surgery. *J Clin Oncol* 2001;**19**(11):2821–8.
20. Simon T, Hero B, Bongartz R, Schmidt M, Muller RP, Berthold F. Intensified external-beam radiation therapy improves the outcome of stage 4 neuroblastoma in children >1 year with residual local disease. *Strahlenther Onkol* 2006;**182**(7):389–94.