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Original Article

The efficacy of delayed surgery in children with high-risk neuroblastoma

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ABSTRACT

Context: Surgery is an important part of treatment in children with neuroblastoma; however, exact timing is unclear. Both initial and delayed surgery was suggested as the best by numerous studies.

Aims: Thus, we aimed to investigate the role of delayed surgery on 31 children with high-risk neuroblastoma.

Materials and Methods: Thirty-one children with high-risk neuroblastoma were enrolled into the study.

Statistical Analysis Used: Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) for windows 10.0.

Results: There 'were 15 male and 16 female patients with a median age of 3.0 ± 3.2 years. Primary tumor site was adrenal in 27, non-adrenal in two, pelvic in one, and mediastinal in one patient. MYCN gene was amplified in four and non-amplified in 11 children on totally 15 children with available data. Lactate dehydrogenase was elevated in 30 children. The tumor volumes at diagnosis and before surgery in the whole group were 154.3 and 12.5 mL, respectively. The decline in tumor volume was statistically significant ($P < 0.0001$). Initial surgery was performed in three and delayed in 20 children, and eight children were inoperable. Surgical complication rate was 66.6% (two out of three patients) in initial surgery group; however, the rate was 15% (3 out of 20 patients) in delayed surgery group. The 5-year event-free survival and overall survival rates in the whole group were 44.8% and 50.8%, respectively. Primary tumor area control rate was 95%

Conclusions: In conclusion, the delayed surgery with intensive chemotherapy and radiotherapy has been successful for primary control in high-risk neuroblastoma patients.

KEY WORDS: Childhood, delayed surgery, high risk, neuroblastoma, treatment

INTRODUCTION

Although high-dose chemotherapy regimens and stem cell transplantation made a facilitating effect in the prognosis of advanced stage high-risk neuroblastoma in recent years, the long-term prognosis remains poor.[1] The role of surgery in localized disease is clear; however, exact timing of surgery in the treatment of localized advanced stage neuroblastoma has remained controversial.

Initial resection of the primary tumor with gross total resection enhanced survival in children with metastatic neuroblastoma over 1 year of age.[2] Kaneko *et al.* suggested that there is no need for extensive surgery in the treatment of advanced and metastatic neuroblastoma if supplemented with intensive chemotherapy.[3] Furthermore, in advanced stage high-risk patients, delayed surgery after intensive chemotherapy provides improved rate of total resection, decreased rate of surgical complications with a decrease in the rate of microscopic residual disease, and also provides to avoid from possible radiation therapy.[3-5] Thus, we evaluated the role of delayed surgery on outcome of children with high-risk neuroblastoma in this study.

MATERIALS AND METHODS

This study was enrolled on patients with high-risk neuroblastoma between 2003 and 2008. All the children were under national neuroblastoma chemotherapy protocol (Turkish Pediatric Oncology Group Neuroblastoma Study).[6] The national neuroblastoma protocol for high-risk disease consisted of surgery at the time of diagnosis or if not possible, after eight cycles of chemotherapy. After surgery, the treatment went on with radiotherapy, consolidation, and maintenance chemotherapy. Chemotherapy protocol consisted of ifosfamide, cisplatin, doxorubicin, dacarbazine, etoposide, and cyclophosphamide. [The protocol details were given in Figure 1].

Thirty-one children with high-risk neuroblastoma were enrolled into the study. The criterion for enrollment to high risk was (a) stage 3 and 4 disease, (b) increased *MYCN* gene amplification,

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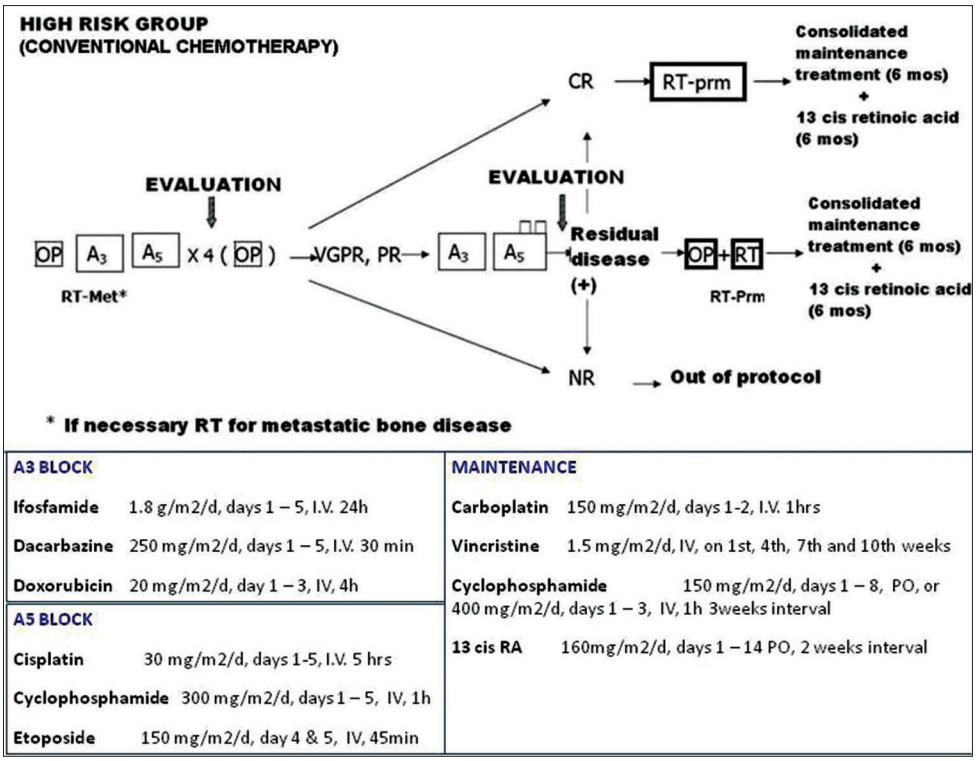

Figure 1: The details of turkish pediatric oncology group neuroblastoma 2003 – high risk conventional chemotherapy protocol

and (c) age older than 1 year. Data including age, gender, stage, histopathology, serum lactate dehydrogenase (LDH), and ferritin levels, *MYCN* gene amplification, tumor volume at diagnosis, and at the time of surgery, primary tumor site (abdominal adrenal, abdominal non-adrenal, pelvic, mediastinal, cervical), surgical modality (total, subtotal, gross residue, microscopic residue), surgical complications, relapses, and detailed radiotherapy information were retrieved from patients medical records. The primary tumor site and extent of disease were determined by physical examination, diagnostic radiologic imaging, and additional bone survey and marrow studies.

Staging was determined with International Staging System (INSS). *MYCN* amplification was defined as a gene copy number >10 by fluorescence *in situ* hybridization (FISH). Serum LDH activity over 450 U/L and ferritin concentration over 140 ng/ml was considered elevated. Initial or delayed surgery was determined with the time of resection done by the surgery team. Initial surgery was done at the time of diagnosis, while delayed surgery was performed after eight or ten cycles of chemotherapy. The definition of surgical resection was defined as; total resection (TR), removal of the tumor completely with no visible tumor from the primary site without microscopic residue; subtotal resection (STR), removal of more than 50% of visible tumor from the primary site but there is visible residue; gross residue (GR), removal of less than 50% of visible tumor from the primary site with visible residue; gross total resection with microscopic residue (GTR-MR), removal of the tumor completely with no visible tumor from the primary site, however, there is microscopic residue. Possible involved or suspicious regional lymph nodes were removed. Tumors were considered unresectable if there was significant involvement of major vascular or neuronal structures and organs. Imaging studies were enrolled at the time of diagnosis, after finishing eight cycles of chemotherapy and at the end of ten cycles.

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) for windows 10.0. Fisher exact test, the Wilcoxon exact rank-sum test, and Chi-square test were used to compare patient characteristics, biochemical and marker data, and complications of the groups. Kaplan and Meier method was used for survival and event free survival (EFS) distribution estimation. The exact log-rank test was used to compare survival and EFS distributions.

RESULTS

There were 31 children with neuroblastoma in the high-risk group. The characteristics of the patients were shown in Table 1. Of the 31, one children had stage 2 with high MYCN amplification (3, 2%), ten stage 3 (32, 3%), and 20 stage 4 (64, 5%) disease. We found no significant difference between the initial and delayed surgery groups in respect of age, gender, serum LDH and ferritin levels, Vanillylmandelic acid (VMA) levels, tumor volume at diagnosis ($P > 0.05$).

Twenty-three patients underwent surgery, whereas eight were inoperable or still under treatment. Three patients underwent initial surgery (two TR, one STR) and delayed surgery was

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Table 1: The demographic and characteristic data of patients with high-risk neuroblastoma

Characteristics	*n* (%)
Gender (*n*=31)	
Male	15 (48.4)
Female	16 (51.6)
Age at diagnosis (*n*=31)	
Median (year)	3.0±3.2
Primary site (*n*=31)	
Adrenal	27 (87.1)
Non-adrenal	2 (6.5)
Pelvic	1 (3.2)
Mediastinal	1 (3.2)
MYCN gene status (*n*=15)	
Amplified	4
Non-amplified	11
LDH (*n*=30)	
<	-
>	30
Ferritin (*n*=28)	
<	14
>	14
VMA (*n*=29)	
<	3
>	26
Surgery (*n*=23)	
Initial	3
Delayed	20

LDH=Lactate dehydrogenase, VMA=Vanillylmandelic acid

performed on 20 patients (ten TR, two STR, and eight GTR-MR). Eight patients who did not undergo a surgical procedure were excluded from further analysis. Surgical complication rate was 66.6% (two out of three patients) in initial surgery group; the rate was 15% (three out of 20 patients) in delayed surgery group. Surgical complication was evident in five (21.7%) of 23 patients who underwent surgery. The complications in initial surgery group were; nephrectomy in one, and spermatic vein injury in one patient; whereas the complications in delayed surgery group were cisterna chyli injury in one patient, renal artery, renal vein injury, volvulus and ileus in one, renal vein, and colonic injury in one patient. The median tumor volume at diagnosis and before surgery was 154.3 and 12.5 ml, respectively in the whole group and the decline in tumor volume was significant ($P < 0.0001$).

The median follow-up time in patients underwent surgery was 2.08 years (0.16–5.83). Seventeen (73.9%) patients were alive, and six (26.1%) patients died. Seven (30%) of the 23 patients were relapsed and five of the relapsed were died. Relapse localizations were bone in three patients, bone marrow in one, brain in two, and primary tumor area in one patient. Primary tumor area control rate was 95% (just one in 20 patients who underwent delayed surgery and completed the treatment had relapsed in the primary region).

The 5-year EFS and overall survival (OS) rates in the whole group were 44.8% and 50.8%, respectively. The 5-year OS estimates were 52.5% in delayed surgery groups. Five-year OS estimates were 21.4% and 67.3% in boys and girls, respectively (log rank $P = 0.03$). Five-year OS estimates were 48.9%, 100%, and 100% in abdominal-adrenal, abdominal-non-adrenal, and pelvic, respectively (log rank $P = 0.0001$). Five-year OS estimates were 41.6% and 48.7% in stage 3 and stage 4 patients, respectively (log rank $P = 0.42$). Five-year OS estimates were 25% and 66.7% in low copy MYCN and high-copy patients, respectively but the analysis can be done only on 15 patients because of unavailable data (log rank $P = 0.70$). Five-year OS estimates were 63%, 66.6%, 62.5%, and 21.8% in TR, STR, GTR-MR, and no surgery groups, respectively (log rank $P = 0.007$).

DISCUSSION

There are numerous studies aiming to find the role of delayed surgery in high-risk neuroblastoma; however, the results were contradictory.[2,7,8] The study from Memorial Sloan Kettering Cancer Center (MSKCC) mentioned that initial surgery was successful in patients with high-risk neuroblastoma.[5] The authors from Japan reported that the success rate decreased in normal N-MYC levels.[9] Our aim was to investigate the efficacy of the delayed surgery in neuroblastoma.

Although intensive chemotherapy regimens and autologous bone marrow transplantation improved survival in high-risk neuroblastoma,[10] children with high-risk neuroblastoma have poor prognosis. Chemotherapy reduces the tumor to a resectable size by forming a more fibrous and less vascular tumoral structure. Thus, delayed surgery was found more effective on survival than initial surgery.[3,5,11] We found 52% of survival rate in children with delayed surgery group. Primary tumor control rate was as high as 95% in our study. This rate was due to intensive chemotherapy followed by surgery and radiotherapy. There was only one relapsed case in primary tumor area of the patients with delayed surgery. The other cases with relapse were from bone, bone marrow, and central nervous system (CNS). Our protocol effectively controls primary area.

Gross TR at the time of diagnosis was found to be associated with improved survival.[2] However, LaQuaglia *et al.* reported a survival benefit from GTR regardless from time of surgery.[5] These findings were all supported the hypothesis that type of surgery (especially GTR) is more efficient on survival than time of surgery. We also found three-fold increased survival rates in GTR group as compared with patients without surgery; however, the survival rates were nearly similar in TR, STR, and GTR groups. Surgery alone is also not effective in the treatment of patients with high-risk neuroblastoma because of residual microscopic disease in all patients except stage I. It should be augmented with local radiotherapy to prevent local recurrence. Moreover, surgery has no effect on metastatic disease. Thus, current treatment modality in patients with high-risk neuroblastoma is delayed surgery after several courses of intensive chemotherapy. Gross TR protects local recurrence and disease progression and increases survival.

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The GTR at diagnosis was found to be associated with increased rate of complications.[2] Great vessel injury, infection, diarrhea, blood loss, and peritumoral or adjacent organ injury were the most reported complications in the surgery of neuroblastoma.[12] The rate of surgical complications vary from 11.9% to 44.1%.[12,13] In our study, the surgical complications were gathered in a small group as vessel and adjacent organ injury and the complication rate was 21.7% in the whole group. The complication rates in the initial and delayed surgery groups were 66.6% and 15%, respectively. The results of our study clearly confirmed that delayed surgery decreased the complication rates. Another factor that may influence the low complication and increased GTR rates is the decrease in tumor volume. There was a 92% reduction in tumor volume after intensive chemotherapy in our delayed surgery group. After an increase in survival with intensified chemotherapy regimens with/without additional stem cell transplantation,[9,14] the necessity of initial surgery becomes controversial. Kaneko *et al.* suggested that there is no need for an extensive surgery during the treatment of advanced neuroblastoma.[3] An attempt to achieve radical excision of the tumor in advanced cases is always risky and very challenging. Thus, Koh *et al.*[15] suggested aggressive surgery in cases that surgery can succeed to remove all metastatic disease. Additionally, the authors advised the surgeons to convince that the effort invested is worthwhile for the patient. So, a delayed surgery with a more small a resectable tumor seems to be more feasible. In conclusion, surgery (total or gross total) has a definitive role on survival in children with neuroblastoma like other solid tumors. Delayed surgery is helpful in increasing the totally resectability of the tumor, decreasing tumor volume and surgery-related complications.

REFERENCES

1. Ladenstein R, Potschger U, Hartman O, Pearson D, Klingebiel T, Castel V, *et al*.; EBMT Paediatric Working Party. 28 years of high-dose therapy and SCT for neuroblastoma in Europe: Lessons from more than 4000 procedures. Bone Marrow Transplant 2008;41 Suppl 2:118-27.
2. McGregor LM, Rao BN, Davidoff AM, Billups CA, Hongeng S, Santana VM, *et al*. The impact of early resection of primary neuroblastoma on the survival of children older than 1 year of age with stage 4 disease: The St. Jude children's research hospital experience. Cancer 2005;104:2837-46.
3. Kaneko M, Ohakawa H, Iwakawa M. Is extensive surgery required for treatment of advanced neuroblastoma? J Pediatr Surg 1997;32:1616-9.
4. Kuroda T, Saeki M, Honna T, Kumagai M, Masaki H. Late complications after surgery in patients with neuroblastoma. J Pediatr Surg 2006;41:2037-40.
5. La Quaglia MP, Kushner BH, Heller G, Bonilla MA, Lindsley KL, Cheung NK. Stage 4 neuroblastoma diagnosed at more than 1 year of age: Gross total resection and clinical outcome. J Pediatr Surg 1994;29:1162-5.
6. Olgun N, Gunes D, Aksoylar S, Varan A, Erbay A, Hazar V, *et al*. The Turkish Pediatric Oncology Group Neuroblastoma 2003 (TPOG-NBL-2003): Treatment results of the high risk group. Congress of the International Soicety of Paediatric Oncology. 40th ed. SIOP Abstract Book. Berlin, Germany; 2008. p. 140.
7. Castel V, Tovar JA, Costa E, Cuadros J, Ruiz A, Rollan V, *et al*. The role of surgery in stage IV neuroblastoma. J Pediatr Surg 2002;37:1574-8.
8. Moss TJ, Fonkalsrud EW, Feig SA, Lenarsky C, Selch M, Wells J, *et al*. Delayed surgery and bone marrow transplantation for widespread neuroblastoma. Ann Surg 1987;206:514-20.
9. Suita S, Tajiri T, Sera Y, Takamatsu H, Mizote H, Nagasaki A, *et al*. Improved survival for patients with adavnced neuroblastoma after high-dose combined chemotherapy based in part on N-myc amplification. J Pediatr Surg 2000;35:1737-41.
10. Matthay KK, Reynolds CP, Seeger RC, Shimada H, Adkins ES, Haas-Kogan D, *et al*. Long-term results for children with high-risk neuroblastoma treated on a randomized trial of myeloablative therapy followed by 13-cis-retinoic acid: A children's oncology group study. J Clin Oncol 2009;27:1007-13.
11. Kiely EM. The surgical challenge of neuroblastoma. J Pediatr Surg 1994;29:128-33.
12. Canete A, Jovani C, Lopez A, Costa E, Segarra V, Fernandez JM, *et al*. Surgical treatment for neuroblastoma: Complications during 15 years' experience. J Pediatr Surg 1998;33:1526-30.
13. Shamberger RC, Allarde-Segundo A, Kozakewich HP, Grier HE. Surgical management of stage III and IV neuroblastoma: Resection before or after chemotherapy? J Pediatr Surg 1991;26:1113-7.
14. Kaneko M, Tsuchida Y, Mugishima H, Ohnuma N, Yamamoto K, Kawa K, *et al*. Intensified chemotherapy increases the survival rates in patients with stage 4 neuroblastoma with MYCN amplification. J Pediatr Hematol Oncol 2002;24:613-21.
15. 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;21:69-72.

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