

JOURNAL CLUB SUMMARY

6/30/04 – Neuroblastoma

(attendees: Breuer, Moss, Seashore, Touloukian, Tashjian, Silverman, Jose, Schaefer, Chaar, Szobota, Henry)

- I. Strother D, Van Hoff J, Rao RV, Smith EI, Shamberger RC, Halperin EC, Murray KJ, Castleberry RP. Event-free survival of children with biologically favourable neuroblastoma based on the degree of initial tumour resection: results from the Pediatric Oncology Group. Eur J Cancer 33:2121-2125, 1997.

Presented by Jochen Schaefer, MD

Reported	Not App.	REPORTING DETAIL – METHODS SECTION	Comments
yes		A clear description of study design	Retrospective analysis
Yes		The number and practice type of institutions where cases were performed	List of institutions supplied
No		Number of surgeons who actually operated in study	
No		A statement as to whether the same surgeon operated on pts from different treatment groups or just one group	
No		The precise timeline during which patients were treated	
Partial		A clear description of how patients were selected into study	Stage 2B or 3 mycn non-amplified neuroblastoma, treated on protocol 8742 or 9244, and rx and follow-up data were available
yes		The number of eligible patients at the study sites excluded during the study	62 patients enrolled on protocol; 11 were excluded due to mis-staging; 2 had lack of rx data
no		A clear description of the study population	No demographics or any information given on the patients
yes		A clear description of the relevant diagnostic criteria used to identify cases	
no		A clear description of critical aspects of operative technique and peri-operative care	
no		Statement as to whether any attempts were made to standardize operative technique or peri-operative care	
		RESULTS	
Yes		Appropriate measures of central tendency of all relevant demographic and baseline variables	
Yes		Range and median for length of follow-up reporting	
Yes		Relevant outcome variables are presented with appropriate measures of range and variability	
		Methods for measuring outcomes of interest are clearly described	
No		Statement is made whether any data is missing (and how missing data is addressed)	
No		Number and appropriate details regarding all complications	
		IF MORE THAN ONE TREATMENT GROUP	
No		Appropriate measures of central tendency for all relevant demographic and baseline variables for all treatment groups	No demographics given
No		The range and median for length of follow-up reporting for each treatment group	2 yr follow up data given
No		A precise timeline during which all patients were treated for each group	
Yes		Outcome variables being compared between groups are presented with appropriate measures of variability (eg standard deviation)	
Yes		Measure of type I error: (p-values) for comparison statistics are presented with actual values if p=0.01 or larger (eg. P=NS and p<0.05 are not acceptable).	
No		Type I error cont: Confidence interval presented	

No		Measures of type II error should not be >0.2 (study should have at least 80% power)	
Yes		A description of how patients were selected into each treatment group	Determined based on their resection - either complete or incomplete
No		A statement is made as to whether the same surgeons operated on patients from different treatment groups	

Summary: A retrospective analysis of 49 patients with stage 2B or 3 neuroblastoma treated under POG protocol 8742 and 9244. Survival examined and compared based on the extent of their surgical resection.

Result summary:

Table 1: Estimated two-year event-free survival following complete and incomplete resection. No statistically significant difference in EFS curves for the two groups despite an observed trend for better survival in those with complete resection. P-value was 0.259.

Figure 1: Survival curve for table 1.

Table 2: Event free survival estimates based on histology

Table 3: Event-free and overall survival for patients on each protocol and combined.

Discussion: It is hard to determine whether we can apply this study to our patients because no demographic details about the patients were given. Also, it is very important to know whether the same surgeons operated on those patients with complete versus incomplete resections as this is clearly relevant to outcome, but this information was not supplied.

The power of this is low given that there were only 49 patients on whom they completed the analysis. It is unclear whether there were enough patients to show a difference between the two groups, therefore. Since the power is low, trends are important to notice and the trends seem to show that a more complete resection is important. This has not been proved with a statistical significance, but the trend should be acknowledged.

They have addressed two variables based on Shimada classification and completeness of resection. Could it be that all the patients with incomplete resection had poor histology - data was there but they did an incomplete analysis of this variable. What about looking at does unfavorable histology lead to incomplete resection? Without a more complete analysis of outcome and correlation of the ability to completely resect the tumor with the histology of the tumor and other variables it is not possible to truly tell about the impact of complete resection on outcome due to the possibility of confounding.

II. Powis MR. The effect of complete excision on Stage III neuroblastoma: a report of the European neuroblastoma study group. J Pediatr Surg 31:516-619, 1996.

Presented by Jason Szobota, MD

Reported	Not App.	REPORTING DETAIL – METHODS SECTION	Comments
no		A clear description of study design	Retrospective review
yes		The number and practice type of institutions where cases were performed	29 centers but type not addressed
No		Number of surgeons who actually operated in study	Not reported
no		A statement as to whether the same surgeon operated on pts from different treatment groups or just one group	
Yes		The precise timeline during which patients were treated	1982-1992
yes		A clear description of how patients were selected into study	Evans and INSS for staging; CT, US, bone scans and BM aspirations
Yes		The number of eligible patients at the study sites excluded during the study	Insufficient data, some not resected
Yes		A clear description of the study population	
Yes		A clear description of the relevant diagnostic criteria used to identify cases	See above
No		A clear description of critical aspects of operative technique and peri-	

		operative care	
No		Statement as to whether any attempts were made to standardize operative technique or peri-operative care	
		RESULTS	
No		Appropriate measures of central tendency of all relevant demographic and baseline variables	
Yes		Range and median for length of follow-up reporting	6.8 yr median (-11.6)
No		Relevant outcome variables are presented with appropriate measures of range and variability	No CI given except for one measure of survival
Yes		Methods for measuring outcomes of interest are clearly described	
Yes		Statement is made whether any data is missing (and how missing data is addressed)	In methods: tried to recollect data if any missing
No		Number and appropriate details regarding all complications	

Summary: A retrospective review of 202 patients with stage III neuroblastoma registered with the European Neuroblastoma Study Group that attempts to determine the effect of complete excision on event-free and overall survival.

Results summary:

Table 1: Number of children with complete resection (47), 75%-99% resection (49) and less than 75% resection (27).

Complete excision (29), macroscopic residuals (52%) and microscopic residual (23)

Figure 1: Distribution by tumor site

Figure 2: Overall survival curve

Figure 3: Overall survival curve according to extent of surgical resection (74% for 100% resection vs <100% 59%, p=0.11)

Figure 4: Overall survival curve according to histological excision subgroup (89% for complete excision vs 58% for incomplete, p=0.003)

Discussion:

This paper found that complete excision showed a statistically significant treatment advantage for overall survival. However, in determining if the results are valid, it must be remembered that these patients were not randomized into treatment groups. Their groups are the results of what was possible at surgery. Therefore, there is potential selection bias, as it is likely that more favorable tumors are more easily resectable and those that couldn't be completely excised or resected likely differed in histology or other characteristics from those that could. Furthermore, it does not seem a truly legitimate conclusion to say that what is needed is for surgeons to try harder to do a complete resection. Presumably, all surgeons in this study and others try to do the most complete resection possible. And, these patients had cycles of chemotherapy first as well, so that this should be the most complete resection possible. Unfortunately there was no power calculation and no confidence intervals were shown, so it is not possible to determine how precise this data is. No demographics on the patients were presented, so comparison to other patients is difficult, though one can presume that since this paper is from ENSG it represents most of the children with neuroblastoma treated by cancer centers in Europe.

III. Matthay KK, Villablanca JG, Seeger RC, Stram DO, Harris RE, Ramsay NK, Swift P, Shimada H, Black CT, Brodeur GM, Gerbing RB, Reynolds CP. Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy, autologous bone marrow transplantation, and 13-cis-retinoic acid. NEJM 341:1165-1173, 1999.

Presented by David Tashjian, MD

Reported	Not App.	REPORTING DETAIL – METHODS SECTION	Comments
Yes		A clear description of study design	Double randomized controlled trial
Yes		The number and practice type of institutions where cases were performed	Children's cancer group
No		Number of surgeons who actually operated in study	
Yes		The precise timeline during which patients were treated	1/1991-4/1996
Yes		A clear description of how patients were selected into study	Newly diagnosed high risk neuroblastoma
Yes		The number of eligible patients at the study sites excluded during the study	539 eligible, 379 underwent first randomization, 118 nonrandomly

			assigned (not clear why), 42 no group (with reasons given in text)
Yes		A clear description of the study population	
Yes		A clear description of the relevant diagnostic criteria used to identify cases	
No		A clear description of critical aspects of operative technique and peri-operative care	
No		Statement as to whether any attempts were made to standardize operative technique or peri-operative care	
		RESULTS	
Yes		Appropriate measures of central tendency of all relevant demographic and baseline variables	See table 1
Yes		Range and median for length of follow-up reporting	
Yes		Relevant outcome variables are presented with appropriate measures of range and variability	
Yes		Methods for measuring outcomes of interest are clearly described	
Yes		Statement is made whether any data is missing (and how missing data is addressed)	
yes		Number and appropriate details regarding all complications	Toxicities of treatment presented
		IF MORE THAN ONE TREATMENT GROUP	
Yes		Appropriate measures of central tendency and variability (ie. Median or mean and SE) of all relevant demographic and baseline variables	
Yes		The range and median for length of follow-up reporting for each treatment group	
Yes		A precise timeline during which all patients were treated for each group	
Yes		Outcome variables being compared between groups are presented with appropriate measures of variability (eg standard deviation)	
Yes		Measures of type II error (p-values) for comparison statistics are presented with actual values if p=0.01 or larger (eg. P=NS and p<0.05 are not acceptable)	
Yes		A description of how patients were selected into each treatment group	Randomized
No		A statement is made as to whether the same surgeons operated on patients from different treatment groups	
		OVERALL ASSESSMENT	
Yes		Are the results of this study valid	
		What is the magnitude and precision of treatment effect (if a control group was used and this can be determined)	
Yes		Are the results applicable to your patient population	

Summary: A well-designed randomized controlled trial with two randomization periods. Well reported. Analysis was complete with both an intention to treat analysis and analysis based on actual treatment received.

Result summary:

Demographics: Table 1 shows comparisons between the groups for age, stage, serum ferritin, pathology status, MYCN amplification, metastases, bone marrow immunocytologic status and response. The groups did not differ to a significant degree after either the first or second randomization.

Figure 2: Probability of event-free survival among patients assigned to bone marrow transplantation or continuation chemotherapy. Difference in event-free survival was significant between the two groups (34% BMT vs 22% chemo p=0.034) at three years. At three years, a total of 75 out of 379 patients still without an event. Only 32 at five years and 6 at seven years. Overall survival did not differ significantly between the two groups at three years.

Figure 3: Probability of event-free survival among patients assigned to receive 13-cis-retinoic acid or no further treatment. Difference in event-free survival was significant between the two groups (46% 13-cis-RA vs 29% no rx p=0.027) at 3 years. Overall survival did not differ significantly between the two groups at three years.

Figure 4: Probability of event-free survival among patients who entered both phases of randomization. Overall event-free survival was significantly better for those patients who received chemo and 13-cis-retinoic acid versus those who received chemo only. However, since these curves are only shown since the time of second randomization, patients who received chemotherapy who did not proceed to second randomization, which is about half the group, (which may be due to failure to respond to treatment) are not included, thus this event-free survival may be overestimated.

Discussion: This paper represents a standard of excellence in randomized trial design and reporting. The authors reached three overall conclusions, all of which were well-supported by their data. These three conclusions are: 1) Event-Free (EF) survival at three years is improved in high risk pts with bone marrow transplantation compared to chemotherapy, and also in those patients who receive 13-cis-retinoic acid 2) Overall Survival similar between two groups though virtually all relapses resulted in death so these rates may end up approaching EF survival 3) retinoic acid improved EF survival regardless of prior therapy particularly in those with minimal residual disease or stage IV with an initial complete response.

The statistical analysis for this paper included both an intention to treat analysis as well as analysis based on actual treatment received. Having both of these analyses was useful to see both the efficacy and efficiency of the treatments.

Overall, a very good paper. From these results, they are predicting that they may see a survival difference in the future from bone marrow transplant but do not have the ability to show it now. However, given the results they do have, the recommendation is for patients with high-risk neuroblastoma to receive high-dose chemotherapy and radiotherapy followed by autologous bone marrow transplantation and treatment with 13-cis-retinoic acid.

IV. Kiely EM. The surgical challenge of neuroblastoma. J Pediatr Surg 29:128-133, 1994.

Presented by Marion Henry, MD

Reported	Not App.	REPORTING DETAIL – METHODS SECTION	Comments
Yes		A clear description of study design	Review of 10 years experience and description of surgical method
Yes		The number and practice type of institutions where cases were performed	One center - Hospital for sick children, London
No		Number of surgeons who actually operated in study	
No		A statement as to whether the same surgeon operated on pts from different treatment groups or just one group	
Yes		The precise timeline during which patients were treated	May 1983 to April 1993
Yes		A clear description of how patients were selected into study	All patients with neuroblastoma
Yes		The number of eligible patients at the study sites excluded during the study	6 pts with insufficient information were excluded
Yes		A clear description of the study population	All children with neuroblastoma, 68 males, 61 females. No ages
No		A clear description of the relevant diagnostic criteria used to identify cases	
Yes		A clear description of critical aspects of operative technique and peri-operative care	Thorough operative description supplied
No		Statement as to whether any attempts were made to standardize operative technique or peri-operative care	
		RESULTS	
No		Appropriate measures of central tendency of all relevant demographic and baseline variables	
No		Range and median for length of follow-up reporting	
No		Relevant outcome variables are presented with appropriate measures of range and variability	

Yes		Methods for measuring outcomes of interest are clearly described	
Yes		Statement is made whether any data is missing (and how missing data is addressed)	No info on 6 pts
Yes		Number and appropriate details regarding all complications	

Summary: This paper by Dr. Kiely is both a case series presentation and a description of operative technique. In this article, he describes the operative technique he has used for ten years in order to get as complete an excision as possible for patients with neuroblastoma. He proceeds to describe his outcomes on those patients treated over a ten year period. There are no comparisons made, no statistical analysis.

Result summary:

Table 1: Stage of patients at diagnosis: 4% I, 8% II, 18% III, 67% IV and 3% IV-S

Table 2: Site of primary tumor: 113 abdominal (83 adrenal, 11 preaortic, 19 other abdominal); 10 thoracic and 6 pelvic

Table 3: Complete resection performed by stage

Table 4: Postoperative complications: diarrhea 24, adhesion/obstruction 5, wound infection 3, ascites 3, hypoglycemia 2. (additionally there were 2 deaths discussed in text but not listed in table 4)

Table 5: Survival by stage

Table 6: Disease-free survivors at >2 years

Table 7: Effect of surgery on survival stratified by stage

Table 8: Survival by site

Discussion: This paper presents a case series and a report of procedure which shows that resection is possible in most patients. However, despite the ability to get radical clearance of the tumor, there has not been an increase in survival in patients with advanced disease. The authors conclusions are very fair and worth noting - despite his attempts and long practice at complete resections for this tumor, he reports that "the results support the value of surgery in curing patients with localized disease. Data supporting the value of surgery in advanced disease are contradictory. At the very least, the surgery is challenging for the surgeon, who will need to be convinced that the effort invested is worthwhile for the patient. The lack of convincing data erodes the determination of even the most committed surgeon. The results reported herein suggest that local control can be achieved in a substantial number of children who have advanced disease. Presently, that is all that supports the surgeon in facing this particular challenge."