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Definitive Tumor Resection after Myeloablative High Dose Chemotherapy Is a Feasible and Effective Option in the Multimodal Treatment of High-Risk Neuroblastoma: A Single Institution Experience

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ABSTRACT

Background/Purpose: The delayed local treatment approach (DL) in high-risk neuroblastoma (HR-NB) refers to the process in which tumor resection is performed after the completion of all the courses of chemotherapy, including myeloablative high-dose chemotherapy (HDC). Alternatively, in the conventional local treatment approach (CL), tumor resection is performed during induction chemotherapy. In this study, we compared the surgical outcomes in HR-NB patients treated by CL and DL.

Method: Forty-seven patients with abdominal HR-NB underwent primary tumor resection from 2002 to 2018. The timing of surgery was generally determined by following the trials and guidelines available at the time. The outcomes and surgical complications between the two strategies were compared.

Result: Operation time, blood loss, and postoperative WBC counts were lower in the DL group ($n = 25$) when compared to the CL group ($n = 22$), statistical significance notwithstanding. Major vascular structures were less frequently encased in the DL group tumors, while immediate surgical complications were significantly more frequent in the CL group ($P < 0.05$). Furthermore, the 3-year EFSs were 50.0% and 53.9% in the DL and CL groups, respectively.

Conclusion: DL appears to be a feasible and effective treatment option for HR-NB. Nonetheless, further verifications using larger cohorts are warranted.

Level of evidence: Treatment study, Level III.

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Neuroblastoma, the most frequently encountered extracranial solid tumor during childhood, originates from the sympathoadrenal lineage derived from the neural crest [1]. The outcome of patients with disseminated disease at diagnosis remains dismal despite multimodal treatments, including induction chemotherapy, surgical resection, myeloablative high-dose chemotherapy with hematopoietic stem cell rescue (HDC), and radiotherapy [2–5].

Currently, the standard treatment for high-risk neuroblastoma (HR-NB) consists of a diagnostic biopsy followed by five to seven cycles of conventional induction chemotherapy and consolidation therapy using myeloablative high dose chemotherapy with autologous HDC [2–5]. Previously, surgical resection of the primary site was performed between the courses of the induction chemotherapy, typically after three or four courses (conventional local treatment approach; CL) in Japan [2]; this procedure continues to be included in most of the treatment protocols worldwide. However, the surgical resection of HR-NB is often associated with various complications, such as excessive

Abbreviations: HDC, myeloablative high-dose chemotherapy with hematopoietic stem cell rescue; DL, delayed local treatment approach; CL, conventional local treatment approach; HR-NB, high-risk neuroblastoma; EFS, event-free survival; OS, overall survival; COG, Children's Oncology Group; EBV, estimated blood volume; Gy, Gray; CT, computed tomography; CRP, C-reactive protein; WBC, white blood cell.

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bleeding, concurrent organ removal, chylous leakage, persistent diarrhea, and surgical site infection [6]. These complications may occasionally interfere with the seamless deployment of multimodal treatments, thereby decreasing the dose intensity of the systemic chemotherapy, which may indirectly affect the long-term outcome of the patient. Recently, a novel approach for the treatment of HR-NB involving surgery and radiotherapy of the primary tumor after completion of systemic chemotherapy, including HDC, has been widely accepted in Japan [7–9]. This approach, called the "delayed local treatment" (DL) strategy, allows for the administration of intensive chemotherapy within a shorter time period without prolonging the intervals between each course, thereby increasing the intensity of the systemic treatment. Although the DL strategy has an advantage in increasing the intensity of the systemic treatment, concerns about the safety of tumor resection after HDC exist because HDC is known to induce severe toxicity resulting in sinusoidal obstruction syndrome, capillary leak, prolonged thrombocytopenia, infection, and renal, gastrointestinal, and pulmonary toxicities [2–5]. To date, only a few case series examining the outcome of this unique approach have been published in the literature [7–9].

In the current study, we aimed to clarify the feasibility and efficacy of the DL approach by performing a retrospective institutional review of patients with abdominal HR-NB who were treated with CL and DL; additionally, the outcomes and surgical complications between the two strategies were compared.

1. Patients and methods

1.1. Patients and data collection

A total of 47 consecutive patients newly diagnosed with HR-NB underwent resection of the primary tumor originating from the adrenal gland or retroperitoneal space at our institution between January 2002 and November 2018. Patients who did not undergo tumor resection or were not treated with HDC were excluded from this study. The Children's Oncology Group (COG) criteria [10] were used to define HR-NB. Following institutional approval and registration as a clinical audit, information about the patient's background, histopathological and biomolecular diagnosis, details of chemotherapy, dates of diagnosis, surgery, and autologous hematopoietic stem cell transplantation, image-based tumor characteristics, body weight at surgery, extent of surgery, intraoperative blood loss, intraoperative complications, postoperative complications, perioperative laboratory data, dates of relapse, progression or death, and first site of relapse were retrospectively collected from medical and operation records. Ipsilateral nephrectomy was included as an immediate complication in this study. Estimated blood loss was calculated as 80 × the body weight in children less than 3 years of age and 70 × the body weight in children more than 3 years of age.

1.2. Treatment

Induction chemotherapy was provided to all patients after histopathological confirmation of the diagnosis of neuroblastoma by either biopsy or tumor resection. The treatment procedure followed the clinical trial protocols or guidelines that were widely used during the corresponding period. The induction regimen varied among the patients, although the majority of them received a combination of either cyclophosphamide, vincristine, pirarubicin, and cisplatin or ifosfamide, etoposide, and carboplatin. After five to six courses of induction chemotherapy, the patient was subjected to HDC with autologous hematopoietic stem cell rescue, using a preconditioning regimen consisting of any one of the following: 1) melphalan, etoposide, and carboplatin or 2) melphalan and thiotepa or 3) melphalan and busulfan. Tumor resection was performed at diagnosis or between the courses of induction chemotherapy (CL) or after the completion of all the systemic chemotherapy courses, including HDC (DL). The timing of surgery was determined in a case-by-case manner, based on the consensus of the multidisciplinary team; cases that were enrolled in the clinical trials underwent surgery at the timings recommended in the protocol. The removal of all visible and palpable lesions was attempted during surgery while leaving the adjacent organs as intact as possible. Incomplete resection was accepted in cases with massive vascular involvement. Lymph nodes with apparent tumor involvement were dissected, whereas extensive dissection of sentinel lymph nodes was discouraged. Local radiotherapy was provided at the end of the treatment in the form of intraoperative radiotherapy for the earliest 10 cases (9–13 Gy) and either external beam radiotherapy or proton beam therapy for the subsequent cases (19.8 Gy to the tumor bed with an additional booster dose of 10.8 Gy to the macroscopic residual lesions).

1.3. Evaluation of resection

Pre- and postoperative computed tomography (CT) scans were used to determine the extent of resection *via* cross-sectional primary tumor measurements, as described by von Allmen *et al* [11]. For postoperative evaluation, images from CT scans obtained at least two weeks after surgery were used to distinguish residual tumors from postsurgical effusion or edema. Completeness of resection was initially determined by reviewing the pre- and postoperative CT scans, and classified as complete (no residual disease), near-complete (>90%), significant (>50%), and limited (<50%) in compliance with recent publications on HR-NB resection [11,12]. In the current study, resection categories of ≥90% and <90%, or complete (100%) and incomplete (<100%) were used. Resection evaluation based on the surgeons' operation record was not analyzed in this study because the resection rate was not reported using a uniform definition.

1.4. Image-based measurement and characterization of the tumor

The size of the primary tumor at diagnosis and during preoperative evaluation was measured using multirow-detector CT scans, and the volumetric response of the primary tumor to chemotherapy was assessed. Estimated tumor volume was calculated using the following formula: height × width × depth × π/6. Tumor response ratio was calculated by dividing the volume of the tumor during preoperative evaluation by that at diagnosis.

The encasement of major vascular structures was evaluated with reference to the original version of the image-defined risk factor (IDRF) [13]. IDRF was initially established to predict the surgical risks of localized neuroblastoma and select patients for primary surgical treatment; recently, the criteria have been increasingly used for predicting the surgical outcomes of high-risk neuroblastoma [14,15]. The tumors were recorded as encasement-positive when at least one of the following findings were present: infiltration of the porta hepatis and/or hepatoduodenal ligament, encasement of the branches of the superior mesenteric artery at the mesenteric root, encasement of the origin of the celiac axis and/or origin of the superior mesenteric artery, encasement of one or both renal pedicles, encasement of the aorta and/or vena cava, and encasement of the iliac vessels. Tumors having isolated contact with the renal vessels were excluded from the encasement-positive group.

1.5. Statistical analysis

Comparisons of age, body weight, operation time, blood loss, % blood loss/ EBV, tumor volume, and response ratio between the CL and DL groups were performed using Wilcoxon's rank test. Comparisons of serum C-reactive protein (CRP) levels and WBC counts between the two groups were performed using the unpaired t-test. The proportions of patients with *MYCN* amplification, complete resection, nephrectomy or surgical complications, and preoperative vessel encasement between

the two groups were compared using Pearson's Chi-square test. Correlations between tumor volume or tumor response ratio and the operation time, blood loss, and % blood loss/ EBV were analyzed by Spearman's rank correlation test. Event-free survival (EFS) time was calculated from diagnosis until the first occurrence of relapse, progressive disease, secondary malignancy, death from any cause, or until last contact, if no event occurred. Overall survival (OS) time was calculated from diagnosis until death from any cause, and the log-rank test was used to compare the survival probability between the subgroups. Statistical significance was defined as $P < 0.05$.

2. Results

2.1. Patient characteristics and preoperative status

Radical resection of the primary tumor was performed before HDC (CL group) in 22 cases, including one case undergoing resection at diagnosis and 21 cases undergoing resection between the intervals of the induction chemotherapy. The timing of surgery was after three courses in three, after four courses in 11, and after five courses in seven cases. The resection was performed after HDC (DL group) in the remaining 25 cases. In total, 28 cases underwent primary tumor resection before the year 2014; among them, 22 were categorized into the CL group, reflecting the treatment policy or the clinical trials conducted during that period. During the same period, the DL approach was intentionally used in six cases because, according to the multidisciplinary team, the tumor could not be resected without the risk of causing major vascular injuries or concurrent nephrectomies at the conventional timing. All the cases that underwent surgery in and after 2014 were treated using the DL approach, according to the treatment policy or trial protocol of the corresponding period.

The demographics of the patients included in this retrospective study are summarized in Table 1. The cohort included 29 males and 18 females. No significant differences in age, stage, and *MYCN* status between the CL and DL groups were noted. The interval between the last day of preoperative chemotherapy and surgery was significantly longer in the DL group when compared with the CL group ($P < 0.05$), presumably indicating the longer time required for recovery from HDC-related sequelae. The WBC count immediately before surgery was greater in the DL group, yet transfusion-dependent thrombocytopenia at the time of surgery was more commonly seen in this group ($P < 0.05$).

Table 1
Patient demographics and preoperative status.

	CL ($n = 22$)	DL ($n = 25$)	P value
Age at diagnosis			0.6001
Median ± standard error	40 ± 4.9	43 ± 4.1	
Range	7–122	14–87	
Age at surgery			0.3600
Median ± standard error	42.5 ± 4.8	49 ± 4.2	
Range	13–126	20–94	
INSS staging			0.2137
Stage 3	2	0	
Stage 4	20	25	
Tumor *MYCN* status			0.1428
Amplified	7	14	
Nonamplified	15	11	
Days from last chemotherapy to surgery			<0.0001
Median ± standard error	30 ± 1.7	47 ± 4.2	
Range	9–43	32–142	
WBC count immediately before surgery (×1000/μl)			0.0238
Median ± standard error	1.78 ± 0.4	2.88 ± 0.4	
Range	0.54–7.58	1.12–9.14	
Transfusion-dependent thrombocytopenia at time of surgery			0.0030
Evident	3	14	
Not evident	19	11	

Abbreviations. CL: conservative local treatment group; DL: delayed local treatment group; INSS: International Neuroblastoma Staging System; WBC: white blood cell.

2.2. Surgical outcome and complications

The details and outcome of the surgical procedures are shown in Table 2. One case was treated with laparoscopic adrenalectomy, while the remaining underwent tumor resection through laparotomy. As indicators of surgical stress, postoperative maximum C-reactive protein (CRP) levels were significantly lower and postoperative oral feeding was restarted significantly earlier in the DL group when compared with the CL group ($P < 0.05$). The mean values of the operation time, amount of blood loss, and postoperative maximum WBC counts were also lower in patients belonging to the DL group, although the differences were not statistically significant. Twenty immediate complications were reported in 16 cases and occurred more frequently in the CL group. The complications included eight nephrectomies (CL, 6; DL, 2), six chylous leaks (CL, 4; DL, 2), two persistent diarrheas (CL, 2), one total renal infarction (CL, 1), one partial renal infarction (DL, 1), and one urinoma (DL, 1). The proportion of patients who received ≥90% tumor volume resection or complete tumor resection was not different between the two groups.

2.3. Tumor response and surgical outcome

To evaluate the relevance of the tumor response to the complexity of the surgical procedure, correlations between the tumor volume at

Table 2
Surgical outcome and postoperative courses of tumor resection performed before and after HDC.

	CL ($n = 22$)	DL ($n = 25$)	P value
Procedure performed			0.343
Resection by laparotomy	22	24	
Laparoscopic resection	0	1	
Operation time (min)			0.1006
Median ± standard error	361.5 ± 35.0	300.0 ± 28.5	
Range	103–740	165–766	
Gross blood loss (g)			0.2496
Median ± standard error	230 ± 58.9	156 ± 90.9	
Range	20–1000	0–2195	
Blood loss per estimated circulating blood volume (%)			0.2284
Median ± standard error	21.0 ± 6.1	16.7 ± 6.5	
Range	2.2–118.0	0–139.3	
Immediate complications occurred?			0.038
Yes	11	5	
No	11	19	
Concurrent nephrectomy			0.079
Yes	6	2	
No	16	23	
>90% tumor volume resected on imaging studies			0.867
Yes	19	22	
No	3	3	
Completely resected on imaging studies			0.595
Yes	14	14	
No	8	11	
Maximum postoperative CRP			0.045
Median ± standard error	10.95	6.96	
Range	2.4–25.7	0.66–24.5	
Maximum postoperative WBC count			0.0613
Median ± standard error	5.51	5.03	
Range	1.64–20.58	1.81–13.8	
Postoperative feeding (days)			0.0107
Median ± standard error	4 ± 0.6	3 ± 0.5	
Range	3–15	1–13	
Removal of drainage (days)			0.0548
Median ± standard error	7 ± 0.74	5 ± 1.68	
Range	4–21	2–41	

Abbreviations. CL: conservative local treatment group; DL: delayed local treatment group; CRP: C-reactive protein; WBC: white blood cell.

surgery or the response ratio and the operation time as well as the amount of blood loss were assessed. Larger tumors were associated with increased blood loss per estimated circulating blood volume (P = 0.0286), but not with longer operation time (P = 0.0607). The tumor volume ratio, reflecting the degree of tumor shrinkage in response to chemotherapy, was not correlated with the operation time (P = 0.2466) or % blood loss/ EBV (P = 0.1892). Secondly, we assessed the vascular encasement at surgery and its correlation to the surgical complexity. Tumors with vascular encasement at the time of surgery were associated with significantly greater % blood loss per EBV compared to those without vascular encasement (P = 0.002). Operation times were significantly longer for tumors with vascular encasement (P = 0.0004). Thus, vascular encasement and tumor volume at surgery were the two major predictors of complicated surgeries.

Next, tumor volume, tumor response ratio, and the status of the vascular encasement in the CL and DL groups were evaluated (Table 3). At diagnosis, the tumor volume and the status of vessel encasement were not different between the two groups. Likewise, no differences in tumor volume and tumor volume ratio were noted between the two groups at the preoperative evaluation study. Remarkably, the number of tumors with vessel encasement at surgery was significantly lower in the DL group; 84% of the cases were evaluated as encasement-free at preoperative imaging when compared to 43% in the CL group (P = 0.004).

2.4. Recurrence and survival

Two patients died owing to treatment-related toxicity caused by HDC, and 20 of the remaining 45 patients exhibited recurrence (11/ 21 in the CL group and 9/ 24 in the DL group). The bone/ bone marrow was the site of initial recurrence in 19 patients, including one who presented with simultaneous local relapse; only one patient had an isolated local recurrence in the abdomen. The two patients with local recurrence (one each in the CL and DL groups) were initially treated by ≥90% and 100% resection, respectively, followed by a dose (19.8 Gy) of radiotherapy to the tumor bed.

Patient survival and its correlation with the prognostic factors, including surgery-related variables, were evaluated using the Kaplan–Meier analysis. Twelve out of the most recently diagnosed patients who presented with short (<3 years; 1095 days) diagnosis to analysis periods were excluded for the sake of accuracy. The EFS of the remaining cohort (35 cases; CL, 22 and DL, 13) was 51.4% at three years and 48.6% at five years after diagnosis. OS was 80.0% at three years and 63.5% at five years. No significant differences in EFS and OS rates were observed between the CL and DL groups (3 year EFS, 50.0% *vs.* 53.9%; OS, 81.8% *vs.* 76.9%, respectively). Furthermore, resection rates (between 100% and < 100%, ≥90%, and < 90%), operation time, blood loss/ estimated circulating blood ratio, and concurrent nephrectomy were not related to patient survival (Table 4).

3. Discussion

The results of the present study demonstrated that intra- and postoperative complications were less common in the DL group when compared with the CL group, despite the prolonged myelosuppression represented by thrombocytopenia in the DL group. Interestingly, surgical stress also appeared to be less severe in the DL group, as indicated by the low postoperative CRP levels and early initiation of oral feeding in this group when compared with the CL group. The DL approach for HR-NB may have the additional benefit of reducing the size of the tumor thereby increasing the resectability of the lesion and reducing the surgical risks involved; furthermore, it may also aid in circumventing the occurrence of surgical complications and injuries to the adjacent organs [7]. No difference in the extent of resection of the primary tumor was observed between the CL and DL groups in the current study. However, decreased bleeding, shorter operation time, and fewer surgical complications were evident in the DL group when compared with the CL group, indicating the beneficial effects of HDC on surgery. Evaluation of the imaging studies revealed that tumors with vascular encasement at surgery had a strong correlation with prolonged operation time and increased blood loss. Additionally, large tumor volumes were associated with increased blood loss. Interestingly, although no significant differences in tumor volume at surgery or degree of shrinkage in response to chemotherapy were noted between the two groups, vascular encasement was significantly less frequent in the DL group, which may have, in part, contributed to the decrease in the number of surgical complications in this group. A previous study evaluating the optimal timing of surgery during the courses of induction chemotherapy in HR-NB reported decreased blood loss in patients

Table 3
Evaluation of tumor response to preoperative chemotherapy.

	CL (n = 21[a])	DL (n = 25)	P value
Estimated tumor volume (diagnosis)			0.3090
Median ± standard error	94.1 ± 68.4	129.8 ± 43.2	
Range	4.31–1068.3	5.71–755.6	
Estimated tumor volume (preoperative)			0.3260
Median ± standard error	13.1 ± 9.0	11.4 ± 6.2	
Range	1.2–173.5	0.9–125.3	
Tumor volume ratio (% preoperative/diagnosis)			0.1177
Median ± standard error	16.78 ± 3.30	8.41 ± 5.35	
Range	2.97–52.07	1.55–121.54	
Encasement of major vessels (diagnosis)			0.066
Positive	19	17	
Negative	2	8	
Encasement of major vessels (preoperative)			0.004
Positive	12	4	
Negative	9	21	

[a] The cohort includes all cases that received preoperative chemotherapy with evaluable imaging studies (n = 46). One case in the CL group had a tumor with thoracoabdominal extension and was excluded from the tumor volumetric study since the border of the primary tumor was indefinite.
Abbreviations. CL: conservative local treatment group; DL: delayed local treatment group; INSS: International Neuroblastoma Staging System; WBC: white blood cell.

Table 4
Univariate analysis of event-free and overall survival (n = 35)[a].

Variables	No. of patients	3-year EFS (%)	P value	3-year OS (%)	P value
Timing of surgery			0.9324		0.6382
CL	22	50.0		81.8	
DL	13	53.9		76.9	
Resected tumor volume (≥90% *vs.* <90%)			0.2087		0.3293
≥90%	31	48.3		77.4	
<90%	4	75.0		100.0	
Resected tumor volume (complete *vs.* incomplete)			0.3640		0.6684
Complete	20	45.0		85.0	
Incomplete	15	60.0		73.3	
Operation time			0.1295		0.9784
≥median	18	61.1		88.9	
<median	17	41.2		70.6	
Blood loss per estimated blood volume			0.2266		0.9241
≥median	18	61.1		81.6	
<median	17	41.2		76.5	
Concurrent nephrectomy			0.3983		0.7819
Yes	8	62.5		62.5	
No	27	48.2		85.2	

Abbreviations. CL: conservative local treatment group; DL: delayed local treatment group.
[a] Patients in whom the period from diagnosis to the time of analysis was <3 years were omitted from this analysis.

undergoing resection of the primary tumor after four cycles of chemotherapy when compared with those who were operated after two cycles [6]. We reviewed the images obtained after three cycles of induction chemotherapy of all cases in the DL group and found that only 52% were encasement-free at that point; after subsequent chemotherapy courses (including HDC), an additional eight cases demonstrated no vascular encasement (data not shown). Taken together, these findings suggest that an increase in the number of chemotherapy cycles may provide a safer background for less complicated surgeries. However, the rate of complications could be biased by historical differences in the surgical concepts or skills used in the corresponding era owing to the retrospective nature of this study. The preference for more conservative surgical approaches with increased attempts to preserve the organs has increased in recent years.

HDC was originally intended to serve as consolidation therapy. Therefore, concerns that remnants of a viable primary tumor after HDC could expose the patient to increased risks of recurrence exist. However, the results of the current study showed that the local recurrence, EFS, and OS rates in patients in the DL group were similar to those in the CL group. With regard to the timing of the surgery and the survival of the patient, a previous report by Rojas *et al* comparing surgeries after two, three, four, and five courses of induction chemotherapy demonstrated that patients who underwent primary tumor resection after four courses of chemotherapy had the best prognosis, although the sample size in each group was small and the reason for this difference was not clearly documented [6]. The influence of surgical treatment, before or after HDC, on the survival of the patient is currently being examined in a clinical trial in Japan, and the results of this large-scale study are awaited.

The relation between the extent of resection and survival of HR-NB has been debated for several years [2,11,12,16–24]. In the present study, no significant differences in local recurrence rate, EFS, and OS were noted among the patients treated with different degrees of resection. Recent studies evaluating the impact of tumor resection on local control used <90% and ≥90% volume resections as the cutoff [11,12]. Therefore, we attempted to compare the survival rates of patients who underwent <90% tumor resection with those who underwent >90% resection; however, only four cases in the current study had <90% tumor volume resections, which could lead to less reliable results.

There are several limitations in this study. First, owing to the retrospective nature of the study, the treatment protocol was varied as a result of changes in standard treatments and clinical trials conducted during the study period. However, all cases were treated in a uniform fashion with 5–6 courses of induction chemotherapy followed by autologous HDC, and the intensity of each regime was similar in all the cases. Second, the surgical treatments were not performed by a single surgeon. Hence, the quality of the procedure and the complication rates might have been affected by the skills of the various surgeons. Finally, despite the relatively high number of cases in this institutional review, the sample size is modest and the statistical power is low. A multicenter prospective trial with details from imaging studies and surgical procedures are warranted.

4. Conclusion

In conclusion, surgery after HDC was safely managed with less frequent complications, without affecting the extent of resection, local control rate, EFS, and OS in patients with abdominal HR-NB. The resection of the primary tumor in HR-NB may be postponed until after the completion of all the chemotherapy courses, including HDC, particularly when the presumed risk of vascular injury or normal organ removal remains during the courses of the induction chemotherapy.

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