Results of the Neuroblastoma-2015 protocol for treating neuroblastoma in China: experience from multiple centers

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Abstract

Background: The collaborative efforts of the Chinese Childhood Cancer Organization (CCCG) have led to an improved understanding of NB biology, standardized classification, and stratification strategies, thereby improving outcomes in China. We aimed to assess the NB-2015 protocol developed by the CCCG in 2015 and to evaluate the degree of impact of autologous peripheral blood stem cell transplantation (APBSCT).

Methods: This study enrolled NB patients from seven medical centers in China between 2015 and 2018. In this paper, we retrospectively analyzed the clinical characteristics of 161 patients and used their effect on survival as an outcome measure.

Results: The 3-year event-free survival (EFS) rates were 95.5%, 91.6%, and 51.1% in the low-, medium-, and high-risk groups, respectively. In total, 3 out of 7 (42.8%) patients with stage 2B disease, none of whom had MYCN amplifications, relapsed. A total of 47 of the 78 patients in the high-risk group underwent external-beam radiation to the primary tumor bed (dose ranging from 18 to 36 Gy). There was a significant difference in efficacy between patients who received radiation therapy and those who did not (3-year OS $P = 0.041$). Within the high-risk group, The 3-year EFS rates of the patients with and without APBSCT were 72.6% and 37.1%, respectively ($P=0.008$).

Conclusions: This study showed that satisfactory results were obtained without fatal complications using the NB-2015 protocol. Chemotherapy should be intensified in the stage 2B group. APBSCT can effectively improve the survival rate of NB patients, especially high-risk patients.

Background

Neuroblastoma (NB) is the third most common cancer in children after leukemia and brain cancer[1]. NB is a complex heterogeneous disease that originates from embryonic cells that form primitive neural crests. Its natural history ranges from benign disease to end-stage disease, from spontaneous regression without intervention to highly lethal chemotherapy-resistant diseases. Sympathetic chain and adrenal medulla are the most common primary sites. NB accounts for 7-10% of all pediatric malignancies, but it contributes to nearly 15% of pediatric cancer deaths due to the aggressiveness of the disease and the high probability of metastatic disease at diagnosis[2-3]. More than half of children with NB present with disseminated metastases at the time of initial diagnosis, and most of these patients have advanced disease with a poor prognosis. According to the International Neuroblastoma Staging System (INSS) standard, patients can be divided into low, medium, and high-risk groups, which takes into account biological and clinical characteristics, such as diagnosis age, stage of disease, tumor histology, including the degree of neuroblastoma differentiation and mitotic karyorrhexis index (MKI); molecular markers such as MYCN oncogene amplification. Most patients with INSS stage 1 and 2 NB (usually a low-risk group) can be cured by surgery alone and have a good prognosis, with worldwide consensus[4-5]. However, the treatment of patients with stage 3 and 4 NB, especially in the high-risk population, remains a challenge.

And its results remain poor despite modern treatment strategies. Most studies have shown that the survival rate of NB patients after intensive chemotherapy, surgery, autologous stem cell transplantation, radiation therapy, immunotherapy and other comprehensive treatment is approximately 50%[6-9]. Although modern treatments have improved survival rates, these strategies still fail to eradicate tumors in some high-risk NB patients..

There are also ethnic and geographic differences in the risk status and survival of children with NB[10], and these differences are thought to be caused by genetic and economic differences. For decades, there has been no relatively uniform NB treatment protocol in China; delayed diagnosis, lack of accurate staging, risk stratification and optimal treatment, and abandonment of treatment have resulted in much lower survival rates than in high-income countries. Any of the above factors may contribute to poor survival. In order to standardize the treatment and improve the survival rate of Chinese pediatric cancer patients, multiple medical centers of the Chinese Pediatric Cancer Group (CCCG) have joined our treatment group and used the NB-2015 agreement from 2015. Our NB-2015 protocol recommends combination therapy according to different INSS risk groups, including chemotherapy, surgery, autologous peripheral blood stem cell transplantation (APBSCT), radiotherapy, and cis-retinoic acid maintenance therapy. This paper reports the results of the first retrospective study of NB treatment in various medical centers of the CCCG. A retrospective analysis of NB patients who followed the NB-2015 protocol from 2015 to 2018 was performed to present clinical characteristics and treatment effects and to assess whether the treatment regimen had an effect on survival.

Methods

Patient population

The NB-2015 protocol was implemented by the Department of Pediatric Oncology of Tianjin Medical University Cancer Institute and Hospital in January 2015. This study was approved by the Institutional Review Board of Tianjin Medical University Cancer Institute and Hospital, and all patient guardians provided written informed consent. The medical records of Tianjin Medical University Cancer Institute and Hospital, Qilu Children's Hospital of Shandong University, the Fourth Hospital of Hebei Medical University, Children's Hospital of Soochow University, Wuhan Children's Hospital, Tongji Medical College, Huazhong University of Science and Technology and Shandong Provincial Hospital were searched during January 1, 2015 and July 31, 2018. The follow-up period ended on 31 July 2018.

In this paper, 161 patients with untreated NB were retrospectively studied. Tumors were diagnosed according to INSS criteria. Histological findings were defined by the International Neuroblastoma Pathological Classification (INPC) guidelines as previously described[11]. Pathological sections of all patients were consulted with the Department of Pathology of Tianjin Medical University Cancer Institute and Hospital. Two pathologists in the department made the diagnosis. Biological factors such as histopathological grade, MYCN gene status, and DNA index of the tumor were comprehensively analyzed. Eligible patients were graded according to INSS criteria and divided into low-, medium-, and high-risk

groups according to the Children's Oncology Group (COG) risk stratification scheme (Table 1). NB and adequate clinical data were confirmed in all patients. All patients followed the treatment protocol of the NB-2015 protocol, according to the different risk groups identified by the professional team of pediatric oncologists, including neoadjuvant chemotherapy, surgery, adjuvant chemotherapy, APBSCT, and radiotherapy. Patient characteristics information was analyzed retrospectively (Table 2). The treatment protocol for each group is shown in Figures 1. Local irradiation was given to the high-risk group.

Treatment response

Disease status and response to treatment were classified as complete response, very good partial response (VGPR), partial response (PR), stable disease (SD), or progressive disease (PD) according to published international neuroblastoma response criteria [12]. Complete response (CR) was defined as absence of primary tumor and absence of metastasis on imaging. A very good partial response (VGPR) was defined as a greater than 90% reduction in tumor size. Partial response (PR) was defined as a greater than 50% reduction in the volume of the primary tumor and all measurable metastatic sites. Stable disease (SD) was defined as no new lesions with < 25% increase but < 50% decrease in the size of any lesion; progressive disease (PD) was defined as any pre-existing lesion or any new lesion with greater than 25% increase in size. If surgical resection was attempted, the outcome was recorded according to the International Neuroblastoma Response Criteria: surgery was considered complete, near-complete (leaving minimal residual disease, less than 5%), incomplete (remaining disease between 5% and 50%), or biopsy only (more than 50% remaining).

Statistical analysis

Data were analyzed using SPSS 24.0 statistical software (Chicago, IL, USA). Cumulative survival analysis was performed using the Kaplan-Meier method, and univariate analysis was performed using the log-rank test. Event-free survival (EFS) was calculated from the date of study registration until the date of first relapse, Parkinson's disease, second malignancy, or death from any cause, and if no event occurred, until the date of last contact. Overall survival (OS) and time to event were calculated from the day of study registration until death from any cause or last contact with the patient. APBSCT-related mortality was defined as death from any cause within 100 days after transplantation. All P values were two-tailed, and $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

161 NB patients were treated according to the NB-2015 protocol, including 79 males and 82 females (M: F = 0.96:1). The patient features are listed in table 3. The median age at diagnosis was 37 months (range from 1 to 141 months). Overall, 51 (31.7%) patients were younger than 18 months and 110 (68.3%) patients were older than 18 months at diagnosis. We confirmed that patient age at NB diagnosis was an important independent prognostic factor. Of these, 47 (29.2%) were in the low-risk group, 36 (22.4%) were

in the medium-risk group, and 78 (48.4%) were in the high-risk group. 38 (23.6%) patients had INSS stage 1 disease, 5 (3.1%) patients had stage 2A disease, 7 (4.3%) had stage 2B disease, 32 (19.9%) had stage 3 disease, and 78 (48.4%) had stage 4 disease. Only one patient (0.6%) experienced stage 4S disease. MYCN amplification was observed in 12 analyzed tumors. Among them, only one patient had stage 1 disease, 3 patients had stage 3 disease, and the other 8 patients had stage 4 disease. There were 47 patients (60.2%) in the high-risk group. We found that in our study, only patients with postoperative gross or microscopic residual disease received local irradiation to the tumor bed (doses ranging from 18 Gy to 36 Gy). Thirty-four patients (43.6%) in the high-risk group underwent autologous peripheral blood stem cell transplantation, 18 of whom were treated with busulfan + melfalan (MM) and CBP + VP16 + CTX (CEC). The remaining 16 cases of MM were transplanted. Patients who were scheduled for tandem transplantation received local irradiation after the first transplantation (Table 3).

Treatment outcomes

No patients were lost to follow-up as of the analysis cutoff date. Age at diagnosis is an important independent prognostic factor. There was a significant difference between patients aged < 18 months and ≥ 18 months (3-year OS $P = 0.004$; 3-year EFS $P = 0.000$). The 3-year OS and EFS rates were 100%, 95.5%, 97.2% and 91.6%, and 65.6% and 51.1% in the low-, medium-, and high-risk groups, respectively. In the high-risk group, the 3-year OS rates were 79.0% and 58.3% (0.014) in the graft-free group, respectively. The 3-year EFS rates were 72.6% and 37.1% (0.008) for patients with and without transplantation, respectively (P=0.008) (Figures 2,3). The median survival time (MST) was 26 months (range 7-65 months). No transplant-related adverse effects were observed within 3 years after transplantation. A total of 139 patients had no recurrence and 32 patients had recurrence. Twenty-two patients died of disease progression after relapse. The remaining 10 patients survived, including 3 patients in stage 2B, 1 patient in stage 3, and 6 patients in stage 4. Among these 10 patients, 5 (50%) recovered CR after further treatment. Although patients experienced treatment-induced complications, almost all patients could tolerated intensive treatment. There were no transplant-related complications. Of the 78 patients in the high-risk group, 47 received bedside irradiation of the primary tumor at an irradiation dose of 18 to 36 Gy. There was no significant difference in the 3-year EFS rate between patients who received radiation therapy and those who did not ($P = 0.354$). However, the 3-year OS rate was significantly different between the two groups ($P = 0.041$). Among the patients who underwent total resection, there was also a significant difference in the 3-year OS rate between patients who received and those who did not receive radiation therapy ($P = 0.044$). (Figure 4)

Discussion

Patient age at NB diagnosis is a known important independent prognostic factor. Among the 161 patients, 51 were aged < 18 months and 110 were aged ≥ 18 months at the time of diagnosis. There was a significant difference in OS and EFS rates between the two groups (3-year OS P=0.004; 3-year EFS P=0.000). These results are consistent with previously published findings[13].

Low-risk disease, including stage 1 and asymptomatic stage 2 disease, has a favorable prognosis after noninvasive surgery alone. And surgical resection of the tumor may be the only treatment required in these patients. However, patients with medium-risk tumors may require chemotherapy to shrink the tumor before complete surgical resection can be performed. Chemotherapy can prevent the rapid development of tumors, relieve life-threatening symptoms, and improve the resectability of tumors. The OS rates for low-risk and medium-risk NB patients are estimated to be over 90%, and there is a consistent trend towards minimizing treatment[14]. In our study, the 3-year OS and EFS rates in the low-risk group were 100% and 95.5%, respectively. The 3-year OS and EFS rates in the medium-risk group were 97.2% and 91.6%, respectively. Similar to the results of other studies, patients with completely resected tumors classified as INSS stage 1 rarely relapsed and did not require postoperative chemotherapy.

A total of 32 (19.9%) patients relapsed during treatment or follow-up. Most patients (87.5%, 28/32) were in stage 4, and only 1 was in stage 3. In total, 3 out of the 7 (42.8%) patients classified as INSS stage 2B relapsed. The histopathological types of all three stage 2B patients were negative, and none of them had MYCN amplification. As shown in Figure 2, EFS was significantly lower in patients with stage 2B disease than in those with stage 3 disease, which may be due to less intensive chemotherapy or different genotypes associated with a poor prognosis in this group of patients, resulting in a poor treatment outcome. Molecular genetic techniques are used to stratify patients and optimize treatment.

It has been documented that local radiation therapy can achieve local control in patients with stage 4 or 3 NB by induction chemotherapy and tandem stem cell transplantation[15]. According to our protocol, all patients belonging to the high-risk group require radiation therapy to the primary site and persistent metastases. In our retrospective analysis, we found that only 47 of the 78 patients in the high-risk group received external beam radiation to the primary tumor bed at an irradiation dose of 18 to 36 Gy. On the one hand, the reason for our poor treatment compliance may be that radiation therapy in children is more challenging than in adults given factors such as poor coordination and the need for sedation. On the other hand, this difference can be partly attributed to the lack of professional pediatric radiologists in some medical centers. There was no difference in the 3-year EFS rate between patients who received radiation therapy and those who did not ($P = 0.354$). However, there was a significant difference in 3-year OS between these two patient groups ($P = 0.041$). In particular, patients who underwent total resection had a significant difference in the 3-year OS rate between patients who received radiation therapy and those who did not ($P = 0.044$). Although patients with gross or microscopic residual disease after surgery do not receive local radiotherapy, high-intensity chemotherapy plays a role. Our study shows that local radiotherapy is necessary for patients with NB even after complete resection.

The incorporation of three distinct phases of therapy has improved outcomes for high-risk NB: intensive induction therapy, myeloablative chemotherapy with autologous hematopoietic stem cell rescue, and treatment of minimal residual disease (MRD). In recent years, the survival rate of patients with NB has been increasing due to the intensification of treatment methods[16-18]. Even after these treatments, the relapse rate is still higher than 40%, which leads to the use of treatments such as isotretinoin and monoclonal anti-GD2 antibodies in MRD-positive patients after transplantation[19]. There is a lack of

anti-GD2 monoclonal antibodies in China; therefore, in our NB-2015 protocol, the treatment strategy for NB includes no more than 8 cycles of induction chemotherapy, surgery, combined APBSCT consolidation, and 6 months of post-consolidation therapy with 13 cis-retinoic acid only. Induction therapy plays a key role in the treatment of patients with NB, usually including multiagent intensive chemotherapy and surgical resection of the primary tumor. Over the past few decades, consolidation therapy with stem cell rescue in patients with an initial response to chemotherapy has become the standard of care for high-risk NB in the United States and Europe, largely based on the results of a collaborative group randomized trial comparing the results of this approach with those of chemotherapy alone. The prognosis of patients with high-risk NB is improved by the use of tandem autologous SCT. There are many different drug combinations for hematopoietic stem cell transplantation[20-22]. A clinical trial of NB patients showed that autologous hematopoietic stem cell transplantation was performed with carboplatin/etoposide/cyclophosphamide (CEC) and thiotepa/cyclophosphamide. Other studies have shown other consolidation transplant regimens, including melphalan, MM, and carboplatin/etoposide/melphalan (CEM). A recent convincing report published by the European Neuroblastoma Study Group (ENSG) suggested that MM was associated with greater EFS in a randomized comparison of patients who had good response with induction regimens [23]. Therefore, in our treatment protocol, we recommended MM and CEC tandem APBSCT and observed very good results. In our study, 18 of 34 patients who underwent APBSCT underwent tandem transplantation successfully. The other 16 patients failed to undergo a second APBSCT after the first procedure, due to nonmedical reasons (parental preference, insurance restrictions). Furthermore, we found that tandem transplantation was well tolerated without unbearable complications associated with APBSCT, even including hepatic veno-occlusive disease (HVOD) or sinus obstruction syndrome (SOS). Toxicity was as expected, and implantation was rapid for both cycles. Most importantly, APBSCT significantly improved the survival of patients in the high-risk group. The 3-year OS was 79.0% in the transplant group and 72.6% in the transplant group. There was no significant difference in survival between the two groups, which may be related to the small sample size and short follow-up time.

Conclusion

This study showed that the NB-2015 protocol achieved satisfactory results without the occurrence of fatal complications. Further genotype testing is required in the stage 2B group, and chemotherapy regimens should be enhanced according to different genotypes. Multidisciplinary treatment is necessary, especially for high-risk patients, APBSCT can effectively improve the survival rate. A longer follow-up period is needed to survey the survival rate and incidence of complications for Chinese NB patients who receive chemotherapy, radiotherapy and APBSCT. Treatment outcomes for NB patients have improved; however, the field continues to expand with efforts to develop more targeted treatments for high-risk patients.

Declarations

Ethics approval and consent to participate

Written informed consent and assent forms to participate in the study were obtained from all participating subjects including children, their parents or legal guardians before enrolling in this study. This clinical study was approved by Medical Clinical Committee of Tianjin Cancer Hospital (reference number: bc2018002) according to the ethical principles of the Declaration of Helsinki (1975) including its revision.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors have no conflicts of interest.

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Authors' contributions

Collection of clinical case data and follow-up of patients: JY, JL, FL, LJ, JL, JXL, YPD, JHZ, YJ,YNC, ZYL,DWW and ZLL. Data curation: JY and YJ. Statistical analysis: YJ. Funding acquisition: QZ. Writing–original draft: JY. Writing–review and editing: JL, QZ and YL. All authors have read and approved the manuscript.

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Abbreviations

APBSCT :autologous peripheral blood stem cell transplantation;EFS:event-free survival;OS:Overall survival ;CCCG:Chinese Childhood Cancer Organization ;NB:Neuroblastoma ;INSS:International Neuroblastoma Staging System;MKI:mitotic karyorrhexis index;INPC:International Neuroblastoma

Pathological Classification;COG:Children's Oncology Group;VGPR:very good partial response;PR:partial response;SD:stable disease ;PD:progressive disease ;CR:Complete response;MST:median survival time;ENSG:European Neuroblastoma Study Group .

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Tables

Table 1

COG Neuroblastoma Risk Group Staging System

INSS stage	Age	MYCN amplification	INPC	DNA index	Risk group
1	*0-21y*				Low-risk
2A/2B	< 365d				Low-risk
	≥ 365d−21y	negtive			Low-risk
	≥ 365d−21y	positive	favorable		Low-risk
	≥ 365d−21y	positive	unfavorable		High-risk
3	< 365d	negitive			intermediate-risk
	< 365d	positive			High-risk
	≥ 365d−21y	negitive	favorable		intermediate-risk
	≥ 365d−21y	negitive	unfavorable		High-risk
	≥ 365d−21y	positive			High-risk
4	< 548d	negtive			intermediate-risk
	< 365d	positive			High-risk
	≥ 548d−21y				High-risk
4S	< 365d	negitive	favorable	> 1	Low-risk
	< 365d	negitive		1	intermediate-risk
	< 365d	negitive	unfavorable		intermediate-risk
	< 365d	positive			High-risk

Table 2

Chemotherapy regimens for NB

Risk group	Regimen	Drug	Dosage	Days
Low	CbE	CBP	560 mg/m^2 (< 12 kg: 18 mg/kg)	d1
		VP-16	120 mg/m^2 (< 12 kg: 4 mg/kg)	d1-3
	CbAC	CBP	560 mg/m^2 (< 12 kg: 18 mg/kg)	d1
		CTX	1.0 g/m^2 (< 12 kg: 33 mg/kg)	d1
		E-ADM	30 mg/ m^2 (< 12 kg: 1 mg/kg)	d1
	CE	CTX	1.0 g/m^2 (< 12 kg: 33 mg/kg)	d1
		VP-16	120 mg/m^2 (< 12 kg: 4 mg/kg)	d1-3
	CA	CTX	1.0 g/m^2 (< 12 kg: 33 mg/kg)	d1
		E-ADM	30 mg/ m^2 (< 12 kg: 1 mg/kg)	d1
Intermediate	OPEC	VCR	1.5 mg/m^2 (< 12 kg: 0.05 mg/kg)	d1
		DDP	90 mg/m^2 (< 12 kg: 3 mg/kg)	d2
		VP-16	160 mg/m^2 (< 12 kg: 5.3 mg/kg)	d4
		CTX	1.2 g/m^2 (< 12 kg: 40 mg/kg)	d1
	OPAC	VCR	1.5 mg/m^2 (< 12 kg: 0.05 mg/kg)	d1
		DDP	90 mg/m^2 (< 12 kg: 3 mg/kg)	d2
		E-ADM	30 mg/ m^2 (< 12 kg: 1 mg/kg)	d4
		CTX	1.2 g/m^2 (< 12 kg: 40 mg/kg)	d1
High	CI	CTX	400 mg/m^2 (< 12 kg: 13.3 mg/kg)	d1-5
		Irinotecan	120 mg/m^2 (< 12 kg: 4 mg/kg)	d1-3
	PE	DDP	50 mg/m^2 (< 12 kg: 1.66 mg/kg)	d1-4
		VP-16	200 mg/m^2 (< 12 kg: 6.67 mg/kg)	d1-3
	COA	CTX	1800 mg/m^2 (< 12 kg: 60 mg/kg)	d1-2
		VCR	< 12 mon: 0.017 mg/kg > 12 mon and > 12 kg: 0.67 mg/m^2 > 12 mon and < 12 kg: 0.022 mg/kg	d1-3
		E-ADM	25 mg/m^2 (< 12 kg: 0.83 mg/kg)	d1-3

Table 3

Patients' characteristics (n = 161)

Patients' characteristics		N(%)
Histologic type	Neuroblastoma	112(69.6%)
	Ganglioneuroblastoma	49(30.4%)
Sex	Male	79(49.1%)
	Female	82(50.9%)
Age at diagnosis	< 18 months	12(7.5%)
	≥ 18 months	139(86.3%)
INSS stage	1	38(23.6%)
	2	12(7.4%)
	3	32(19.9%)
	4	78(48.4%)
	4 s	1(0.6%)
Risk groups	Low	47(29.2%)
	Intermediate	36(22.4%)
	High	78(48.4%)

Figures

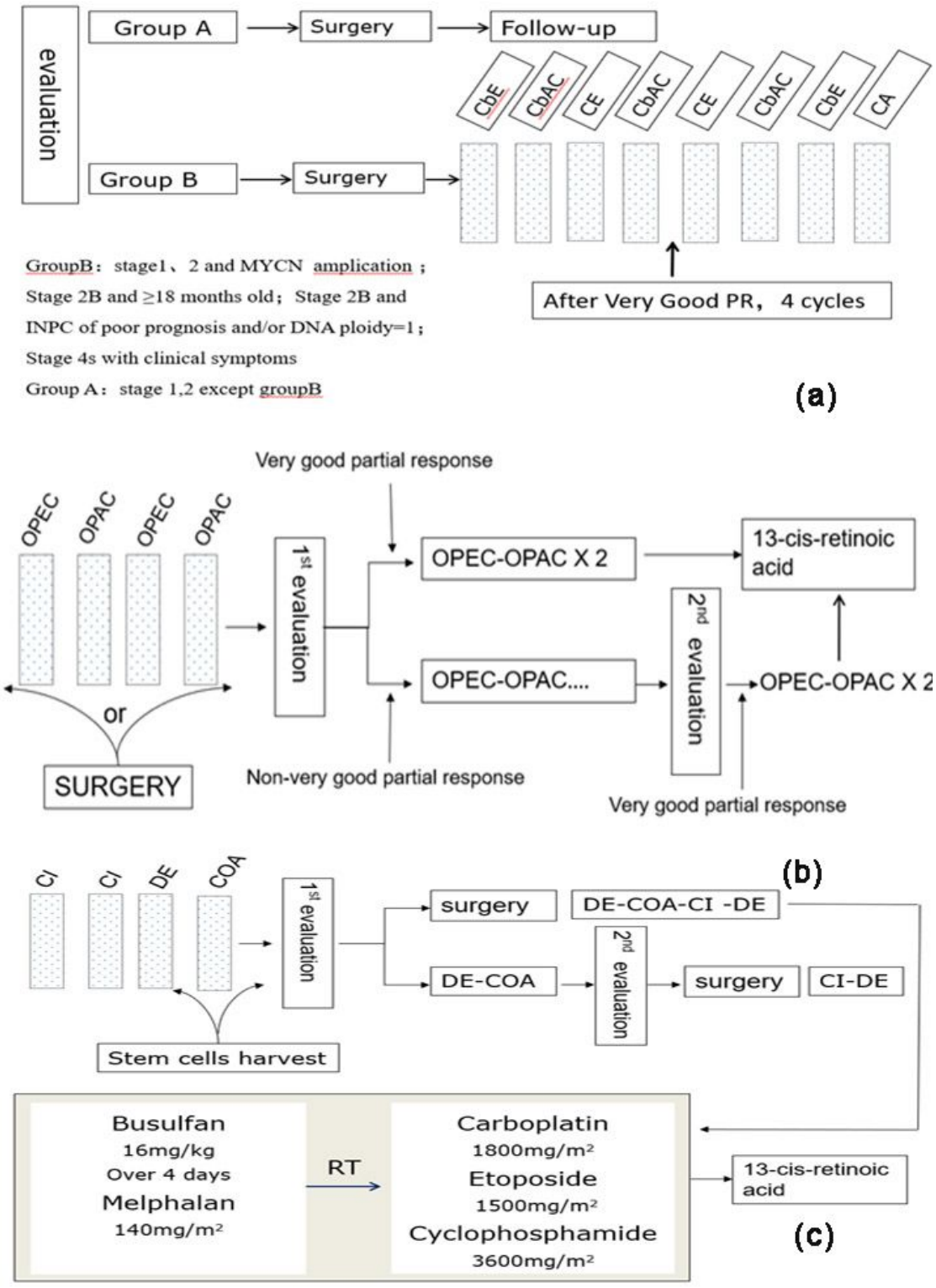

Figure 1

NB-2015 protocol for low-risk group(a), intermediate-risk group(b) and high-risk group(c).

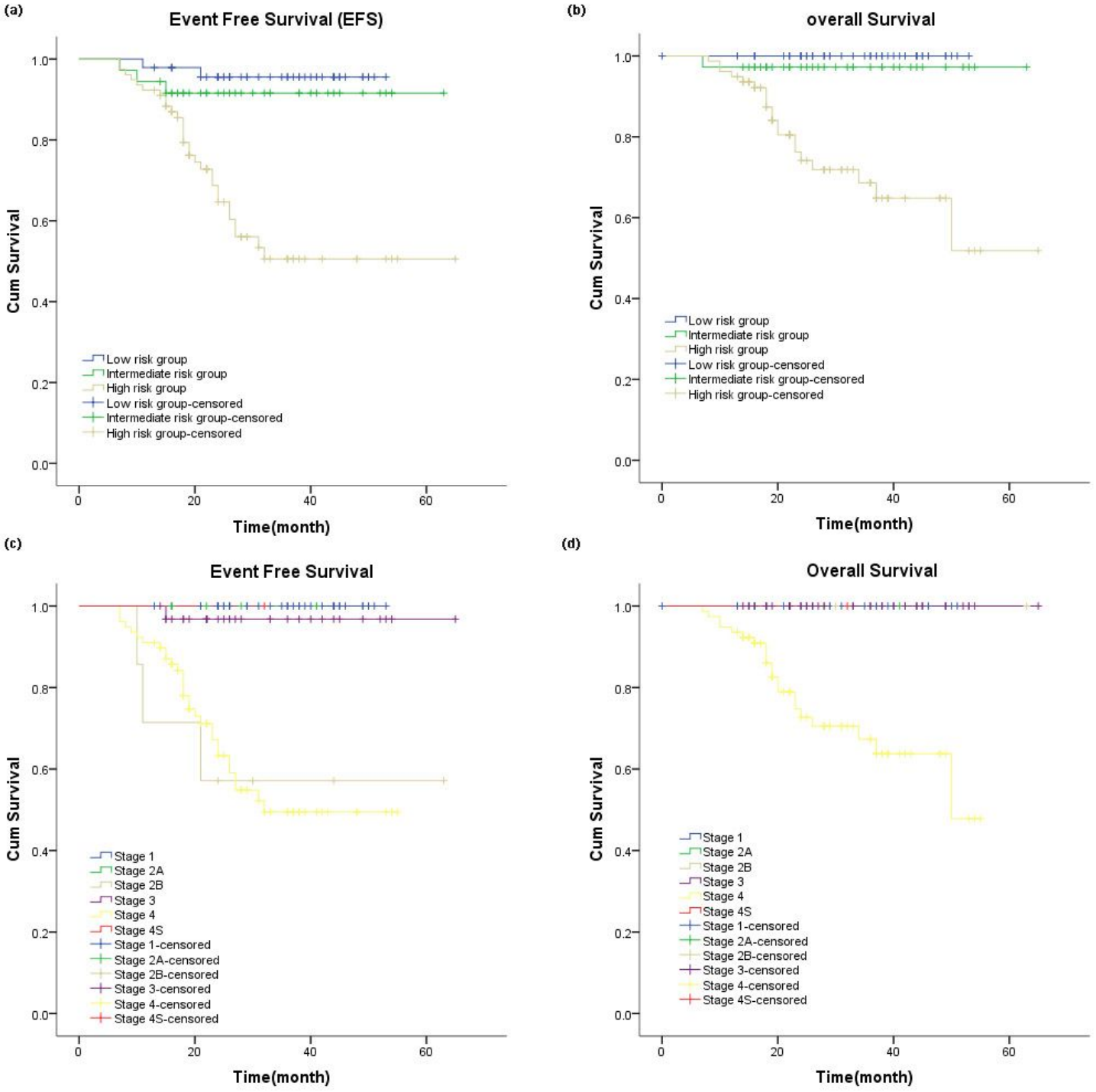

Figure 2

Figure 2.(a): EFS for different risk group; (b): OS for different risk group; (c): EFS for different INSS stage group; (d): OS for different INSS stage group.

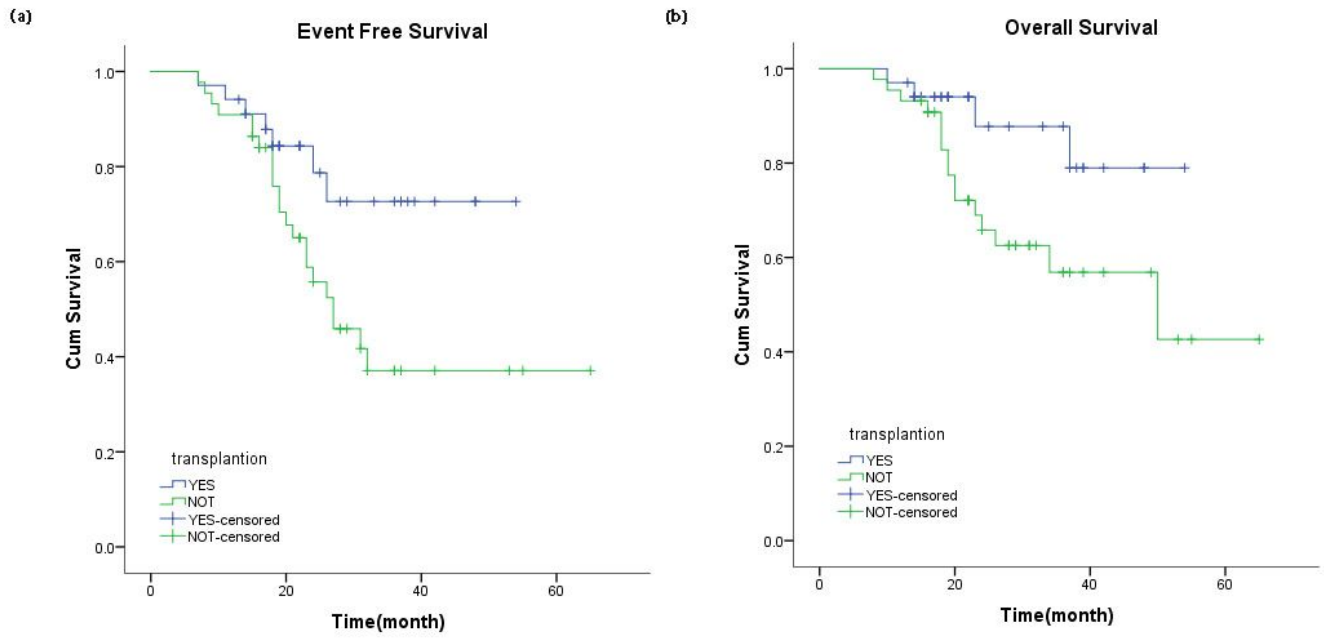

Figure 3

Figure 3.(a): EFS for different risk group; (b): OS for different risk group; (c): EFS for different INSS stage group; (d): OS for different INSS stage group.

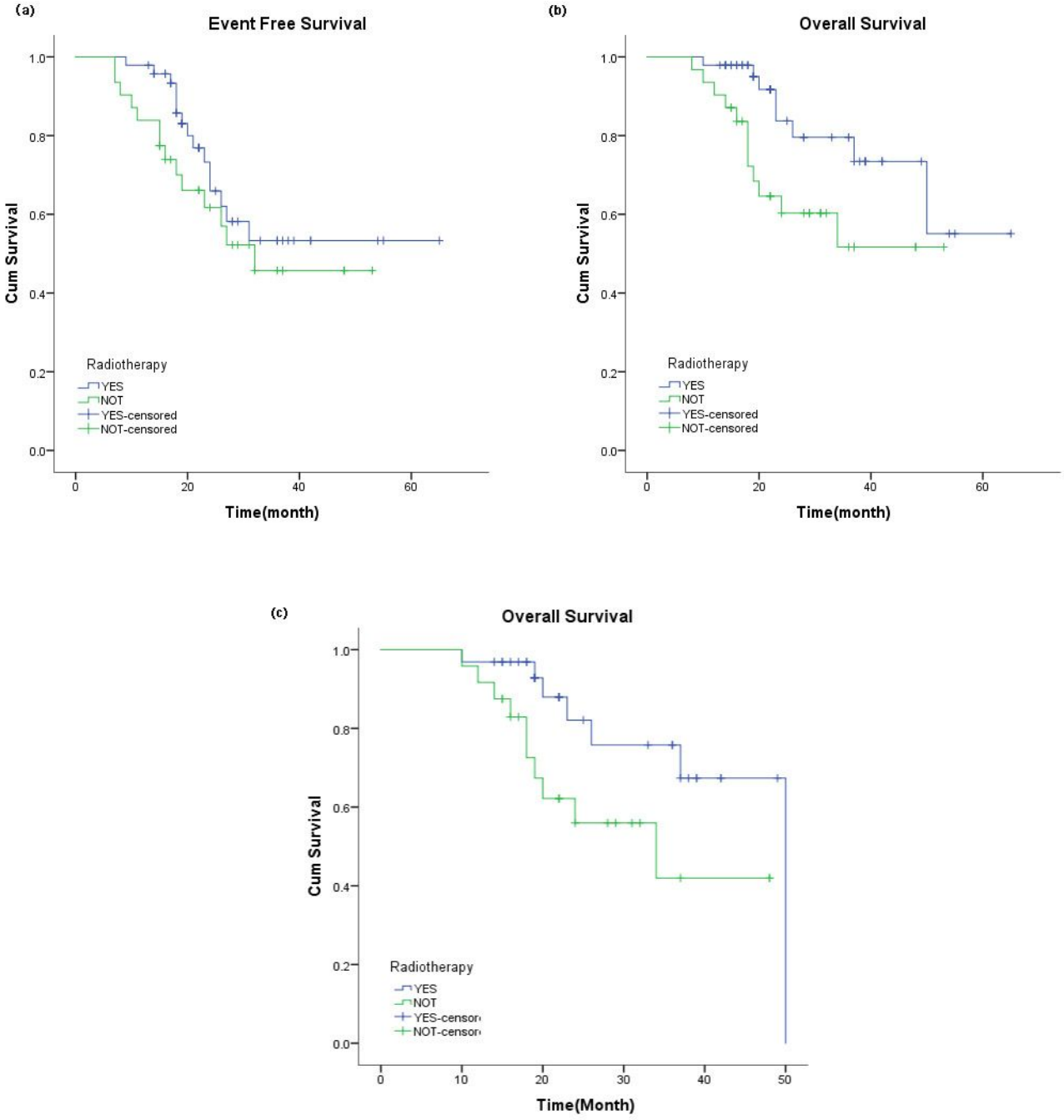

Figure 4

Figure 4.(a): EFS (a) and OS (b) for with and without radiation patients of High-risk group; (c): 3-year OS for high-risk patients with and without radiation after complete excision.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Ethicsapprovalandconsenttoparticipate.pdf

- EditingCertificate.pdf