Long-term outcome of children with neuroblastoma in Shanghai China

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Abstract

Objective This study aimed to assess the development and current state of management and outcome for neuroblastoma (NB) in Shanghai China. Methods The clinical characteristics and survival rates of a large cohort of 717 NB cases in the recent 10 years from two children's medical institutions in Shanghai China were retrospectively analyzed. Results The 8y-EFS and OS of the whole cohort in the 10 years were 67.6±2.2% and 81.2±2.1%. Our risk stratification system was updated twice during the 10 years, forming three periods. The percentage of very low risk (VLR) cohort who accepting only surgery without chemotherapy was increased in 2016-2018 period than the 2010-2015 period and 2008-2009 period. While the 3y-EFS of the three periods were similar (P=0.961). The outcome in VLR and low risk (LR) patients were excellent with 8y-EFS around 92% (VLR=93.0±2.8%, LR= 92.1±1.8%). The outcome in high risk (HR) patients was significantly poorer with 8y-EFS only as 16.6±4.1% even than intermediate risk (IR) patients with 8y-EFS as 69.6±4.4% (P<0.001). Conclusions The revision of our risk stratification system was effective, making an increasing percentage of patients without chemotherapy while with similar EFS rates. The VLR and LR cohort had excellent outcomes, however the HR cohort with most of the mortality remains one of the greatest challenges. Enriching the transplant resources, importing melphalan to make ASCT more available and effective, and importing advanced novel therapies like anti-GD2 antibody and 131I-mIBG are our objectives to improve the survival of the HR patients.

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Methods

The clinical characteristics and survival rates of a large cohort of 717 NB cases in the recent 10 years from two children's medical institutions in Shanghai China were retrospectively analyzed.

Results

The 5y-EFS and 8y-EFS of the whole cohort in the 10 years were 68.7±2.1% and 67.6±2.2%; the 5y-OS and 8y-OS were 81.9±1.9% and 81.2±2.1%. Our risk stratification system was updated twice during the 10 years, forming three periods. The percentage of very low risk (VLR) cohort who accepting only surgery without chemotherapy was increased in 2016-2018 period than the 2010-2015 period and 2008-2009 period. While the 3y-EFS of the three periods were similar (P=0.961). The outcome in VLR and low risk (LR) patients were excellent with 8y-EFS around 92% (VLR=93.0±2.8%, LR= 92.1±1.8%). The outcome in high risk (HR)

patients was significantly poorer with 8y-EFS only as 16.6±4.1% even than intermediate risk (IR) patients with 8y-EFS as 69.6±4.4% (P<0.001).

Conclusions

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Key word : neuroblastoma, children, management, treatment, outcome

Introduction

Neuroblastoma (NB) is the most common extracranial solid tumor in childhood and the most common malignancy in infants, which accounts for more than 7% of malignancies in patients younger than 15 years but is responsible for around 10-12% of all pediatric oncology deaths[1].

NB originates from the primitive cells of the sympathetic nervous system, therefore tumors can develop from anywhere along the sympathetic chain, presenting as a mass arising in the neck, mediastinum, abdomen or pelvis[2]. It is a heterogeneous disease for its broad spectrum of clinical behavior, which reflects different degrees of maturation, varying from spontaneous regression or maturity to a quite aggressive and malignant phenotype[1]. Approximately half of the children diagnosed as NB have metastatic disease with a low probability of cure[3].

Multidisciplinary treatments including surgery, chemotherapy, radiotherapy, auto-transplantation and biotherapy have improved the outcome of children with NB and resulted in 5-year overall survival rate of 80% or so[4, 5]. However, for high-risk NB patients, despite intensive treatment with multidisciplinary therapies, the outcomes remain poor with 5-year long-term survival of less than 50% which would be further decreased by late recurrences and various complications[6, 7].

Children with NB in China are treated basically in the public hospitals where the level of management and treatment varies in different region. The management and outcome of NB in Shanghai represent the domestic advanced level in China. Late presentation, lack of transplant resources and immunotherapy, insufficient multi-disciplinary team work, treatment abandonment due to financial burden are main hurdles for survival in China. In the present study, the cases of 717 children with NB from our two hospitals, Shanghai Children's Hospital and Shanghai Children's medical center (SCMC) in ten years (between September 2008 and August 2018) were retrospectively analyzed, aimed to assess NB management and outcome, implicating the development of NB management in China.

Materials and Methods

Patient

There were 579 newly diagnosed cases of NB from SCMC and 202 cases from Shanghai Children's hospital between September 2008 and August 2018 making a total of 781 cases. 59 patients (7.6%) who lost to follow up within three courses without disease progress were excluded from this study. The final analytic cohort consisted of 717 children accepted the same treatment protocol from SCMC. Informed consent was provided by a parent or guardian for each patient. The study was approved by the ethics committee of Shanghai Children's Medical Center.

Staging and risk classification

According to the International Neuroblastoma System Study (INSS), the patients were divided into 5 stages: 1, 2, 3, 4S, and 4[8]. Risk classification referred to the Children's Oncology Group (COG) classification

system[9] and the International Neuroblastoma Risk Group (INRG)[7] according to age, stage and*MYCN* amplification; image defined risk factors (IDRFs) was involved since January 2016. However, *MYCN* data were almost missing before 2010 because the detection by FISH were not widely used. So, the risk stratification system evolved with the development of our detection technology and international consensus (**SupplementaryFigure 1**).

Treatment

Surgery was performed first for diagnostic reasons or as primary tumor resection except in the patients with NB confirmed by bone marrow (BM) aspiration smear, immune-typing and classical imaging. The requirement for a second surgical resection was based upon the assessment following 4-6 courses of chemotherapy, if complete resection was not performed at the time of diagnosis.

The chemotherapy regimens mainly consisted of the administration of cyclophosphamide, anthracyclines, platinum and other antineoplastic agents. Courses were given every 3 weeks. The drugs and dosages prescribed were reported in **Supplementary Table 1** .

Autologous hematopoietic stem cell transplantation (ASCT) was applied after the whole chemotherapy in patients with intermediate risk (IR) or high risk (HR) diseases when family agree. Radiotherapy was given in children more than 18 months with IR or HR disease after the completion of chemotherapy, surgery and ASCT.

Different treatment arrangements were used according to the risk groups as **Supplementary Table 1** showed.

Data collection and statistical analysis

The overall survival (OS) time was calculated as the time between diagnosis and mortality, while the event-free survival (EFS) time was calculated as the time between diagnosis and relapse, progression, secondary malignancy or mortality, or until the time of the last contact with the patient if none of these events occurred. Last follow-up time was December 31, 2019. The OS and EFS were calculated using the Kaplan and Meier method, and the single-factor analysis was performed by log-rank test. Multiple Cox regression modeling to assess statistical significance of various prognostic factors was employed. The proportional hazards assumption was also confirmed for the final multivariable model. All statistical analyses were performed using SPSS 19.0(Chicago, IL, USA). $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics

From September 1, 2008, to August 31, 2018, a total of 717 patient records were included in the final analysis, clinical characteristics of the patients were delineated in **Table 1** .

There was a male predominance with a male-to-female ratio of 1.19:1, (male 389, female 328). The median age was 31.4 months (range, 0–15.2 years). Five infants were revealed abdominal mass during fetal period by ultrasonography.

Single primary lesion mostly occurred in abdominal (n=436, 60.8%). Three patients revealed mass only in post-orbital tissues and another three children had lesions in rare locations, including two of them in spread soft tissues and one in scrotum. There was one child only revealed metastases in BM without primary lesion. 92 patients (12.8%) had tumors involving two or multiple body compartments, abdominal was involved in 70 of them (76.1%).

The most common metastatic site was bone marrow (n=203, 28.3%) followed by bone at 25.7 % (n =184) and liver at 10.0% (n=72). Metastatic sites also involved lung (n=14, 1.9%), skin and subcutaneous tissue (n=27, 3.8%), brain (n=21, 2.9%) and orbit (n = 11, 1.5%). There were two children had metastatic site in

testes and another two in pancreas. Metastases in breast and spleen were rarities which were revealed in one child separately.

Five patients had paraneoplastic syndromes at the onset of NB, including two children had diarrhea and another three children had diabetes insipidus, cerebellar ataxia and nephrotic syndrome, respectively.

According to INSS patients with stage 4 disease and stage 3 disease were 35.7% (n=256) and 27.3% (n=196) respectively which accounted for the most and second proportions.

Of the 618 patients with available *MYCN* status, 88 patients (14.2%) were *MYCN* positive. Of the 524 patients with available serum lactate dehydrogenase (LDH) data at diagnosis, 327 patients (62.4%) had LDH lower than two times of normal value. 202 of 484 patients with available serum ferritin (SF) data were above normal accounted for 41.7%. 108 of 310 (34.8%) patients with available neuron specific enolase (NSE) data were above six times of normal value.

According to our risk stratification system, patients with low risk (LR) group occupied the highest proportion (n=269,37.5%) and the HR group was second to LR group accounted for 26.5% (n=190).

In 335 patients with IR and HR disease who had indications of taking ASCT, a total of 43 patients (12.8%) accepted it. In 153 HR patients who survived the chemotherapy, only 33 of them (21.6%) chose to accept ASCT.

Treatment outcomes

Up to the cut-off date, the median follow-up time was 28.7 months (range 0.37˜130.8 month). Of the whole 717 patients, 625 patients (87.2%) were alive at the last contact. 182 patients (25.4%) had events of relapse, disease progression or death. The 3y-EFS, 5y-EFS, and 8y-EFS of the whole population were 71.7±1.9%, 68.7±2.1%, and 67.6±2.2%, respectively (**Figure 1**).

The 3y-PFS, 5y-PFS, and 8y-PFS of the whole population were 74.5±1.9%, 71.3±2.1%, and 70.1±2.2%, respectively. 158 patients had recurrence and disease progression with median time of 15.9 months (range: 0.4-102.5 months). 68 patients of them died and the remaining 90 patients were alive in the limited follow-up time (median 0.5 months, range 0-71.4 months), because majority of them abandoned after recurrence and progression leading to lost to follow up.

The 3y-OS, 5y-OS, and 8y-OS of the whole population were 85.7±5.3%, 81.9±1.9%, and 81.2±2.1%, respectively. In addition to the 68 deaths from recurrence and progression, 24 patients were died of treatment related complications including surgery(n=2), infection (n=17), bleeding (n=2), heart failure (n=1), renal failure(n=1), intestinal perforation(n=1), making a total of 92 deaths.

During the ten years of this study, the risk stratification system evolved with the development of our detection technology and international consensus, which was based on factors of age, INSS stage,*MYCN* amplification since Jan, 2010 and IDRFs since Jan, 2016. The percentage of very low risk (VLR) cohort was increased in 2016-2018 period than the 2010-2015 period (18.4% vs 14.5%) and 2008-2009 period (18.4% vs 11.1%), (**Figure 2A**). The 3y-EFS of patients in 2016-2018 period was 72.2±3.6% which was similar with that in 2010-2015 period (3y-EFS=71.5±2.4%) and in 2008-2009 period (3y-EFS=74.0±6.2%, P=0.961) (**Figure 2B**).

According to univariate analysis (**Table 1**), age(P<0.001), sex (P=0.026), primary site (P<0.001), BM metastasis at diagnosis(P<0.001), bone metastasis at diagnosis (P<0.001), *MYCN* status (P<0.001), LDH level (P<0.001), SF level (P<0.001), NSE level (P<0.001), INSS stage (P<0.001) and risk stratification (P<0.001) were significant predictors of EFS (**Supplementary Figure 2**).

The EFS rate of patients aged less than 12 months were significantly higher than that of aged between 12 and 18 months(P=0.003) and aged more than 18 months(P<0.001).

The outcome of patients with single lesion located in abdomen was the worst (8y-EFS =60.9±3.0%) when compared with that of other single locations(P<0.001), which was similar with that of lesions involving

multiple body compartments (P=0.194).

The 8y-EFS for patients with stage 3 disease was 82.1 +-3.1% which was significantly lower than that for patients with stage1 and stage 2 disease (Pstage1 vs stage 3=0.007; Pstage2 vs stage 3=0.001). Stage 4 disease was associated with the worst outcome with 8y-EFS as 27.3+-4.2% when compared with patients with non-stage 4 disease (P<0.001).

The 8y-EFS for patients with VLR was 93.0+-2.8%, that was similar with the patients of LR (8y-EFS 92.1+-1.8%,P=0.520). The outcome in HR patients was significantly poorer with 8y-EFS only as 16.6+-4.1% even than IR patients with 8y-EFS as 69.6+-4.4% (P<0.001).

Of the 190 HR patients, 153 of them survived after chemotherapy and had chances to receive ASCT, only 33(21.6%) of them accepted ASCT with a significantly better 3y-EFS of 53.8+-10.3% than those without ABMT with 3y-EFS of 30.0+-5.1% (P=0.01). However, ABMT didn't show advantages in the long-term outcomes when comparing the 5y-EFS (5y-EFS$_{\text{with ASCT}}$=34.6+-11.2%, 5y-EFS $_{\text{without ASCT}}$=21.3+-5.2%, P>0.05) and 8y-EFS (8y-EFS$_{\text{with ASCT}}$=20.7+-10.1%,8y-EFS $_{\text{without ASCT}}$=21.3+-5.2%, P>0.05) (**Figure 3**).

According to multivariate analysis, independent predictive factors associated with prognosis were age at diagnosis (OR, 2.312, P<0.001), INSS stage (OR,2.212, P=0.004), LDH level (OR,2.717, P=0.002) and SF level (OR,3.158, P<0.001) (**Table 2**).

Discussion

In our present study, we retrospectively analyzed a large cohort of 717 NB cases in the recent ten years from two children's medical institutions in Shanghai which had the most advanced management and treatment in China. We shared the same management protocols which were updated and revised twice from 2008 to 2018. One of the most important part of the updates was risk stratification system which evolved with the development of our detection technology and international consensus. Our risk stratification system was based on factors of age, INSS stage,*MYCN* amplification since 2010 and IDRFs since 2016. With the development of the stratification system, the percentage of VLR cohort was significantly increased from 11.1 % to 18.4%, which means the percentage of patients only accepted observation after surgery without chemotherapy was increased, however the EFS of the three periods was similar. So, the revisions of the stratification system is reasonable and effective. There are still lacking of other genetic assessments such as DNA ploidy and 1p36 deletion status which might have impacted negatively on further improvement of risk stratification.

In this study cohort, with the median follow-up time of 28.7 months, the 3y-EFS, 5y-EFS, and 8y-EFS of the whole population were 71.7+-1.9%,68.7+-2.1% and 67.6+-2.2%; the 3y-OS and 5y-OS and 8y-OS of the whole population were 85.7+-5.3%, 81.9.8+-1.9%, 81.2+-2.1%, which were encouraging. However, in the 90 patients had recurrence or progression without observation of death, 56 of them (62.2%) abandoned and lost to follow-up in 3 months after relapse due to lacking of effective salvage treatment and big financial burden. Only 26/158 (16.5%) of relapsed patients survived for more than one year.

According to our risk classification principals, patients with VLR and LR had the 8y-EFS around 93%; children with IR disease had the 8y-EFS around 70%; however, patients with HR disease had a significantly worse outcome with 8y-EFS less than 20%.The current approach for high-risk NB incorporates induction chemotherapy using a combination chemotherapy regimen, followed by delayed surgery to remove the primary tumor and subsequent myeloablative chemotherapy supported with ASCT[1]. In the present study, although patients with HR disease received ASCT had a much better outcome with 3y-EFS of 53.8+-10.3%. However, ABMT didn't improve the long-term outcomes when comparing the 5y-EFS and 8y-EFS. The questionable effectiveness of ASCT made both clinicians and patients lacking of confidence on it, which leading to low percentage (only 21.6%) of them accepted ASCT. It has been proved by studies [10, 11] that high-dose chemotherapy before ASCT improves EFS compared with treatment not including high-dose chemotherapy in HR patients. Different high-dose chemotherapy regimens have been used in different international trials,

the International Society of Pediatric Oncology European Neuroblastoma Group (SIOPEN) selected to use busulfan and melphalan in their standard practice[12, 13], the Children's Oncology Group (COG) developed carboplatin, etoposide, and melphalan as high-dose chemotherapy[14]. So melphalan is the key drug in conditioning regimen, however it is not available in China which make the outcome of patients accepting ASCT worse than expected. Shortage of transplant resources and the convincing drug of melphalan, and heavy financial burden are main reasons for the low percentage of HR patients to accept ASCT in China.

For high-risk or relapsed cases with dismal outcomes, using novel strategies that are targeted to tumor-specific genetic alternation upfront combining with standard chemotherapeutic agents may improve cure rates without increased toxicity. It is reported that 131I-mIBG used to deliver targeted radiotherapy is active against refractory NB[15-17]. Immunotherapy consisting of anti-GD2 with granulocyte–macrophagecolony-stimulating factor (GM-CSF) and IL-2 are also reported significantly improves outcome for high-risk NB patients by acting on minimal residual disease[18-20]. However, for our high risk or relapsed patients, anti-GD2 antibody and 131I-mIBG were not available in mainland China even in the whole China region currently.

In conclusion, during the recent ten years of study, we improved our stratification system continuously, the long-term outcome proved its effectiveness. Generally, the VLR and LR cohort of NB had excellent outcomes, however the HR cohort with most of the mortality remains one of the greatest challenges to treatment. Enriching the transplant resources to make more HR patients accepting ASCT, importing melphalan to make ASCT more effective, and making advanced novel therapies like 131I-mIBG, anti-GD2 antibody or other immune-therapy available are our objectives to improve the survival of the high-risk cohort.

Conflict of interest

The authors declare no conflicts of interest.

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Author contributions

Jing-Yan Tang and Hui Jiang designed the clinical study and were guarantors of integrity of the entire study. Jie Zhao, Ya-Li Han, Jing-Bo Shao, Ci Pan, Min Xu, Yi-Jin Gao, Dong-Qing Lu, Wen-Ting Hu, and Min Zhou collected the clinical information, Jie Zhao and Ya-Li Han performed the statistical analysis of the clinical data. Jie Zhao prepared and edited the manuscript.

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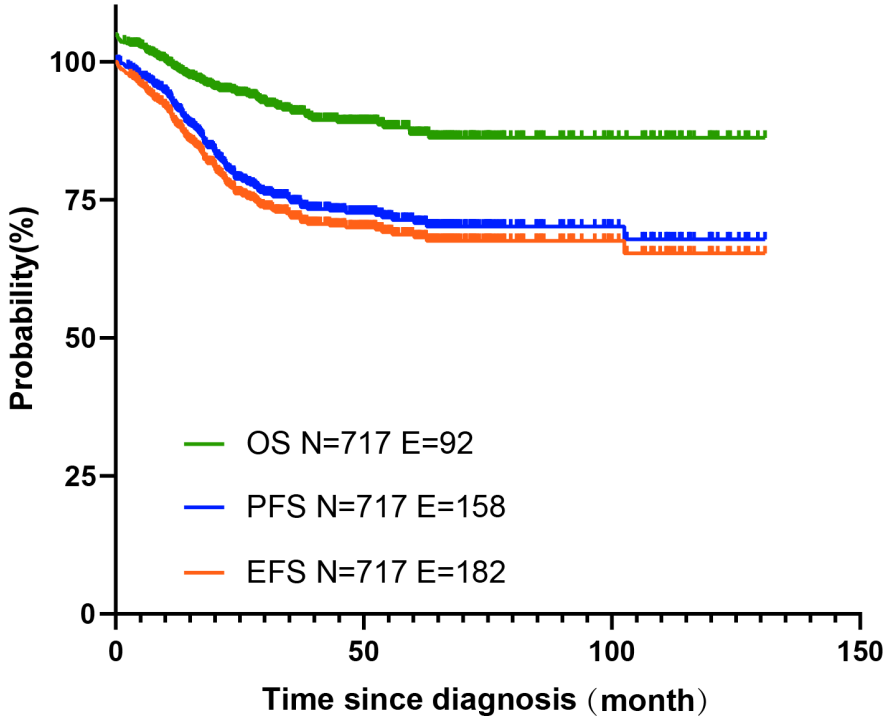
Figure 1. Survival curves of the whole population of 717 children with NB

Figure 2. Composition of risk groups(2A) and EFS curves(2B) in the three periods of development concerns risk stratification

Figure 3. EFS curves in HR patients accepted ASCT.



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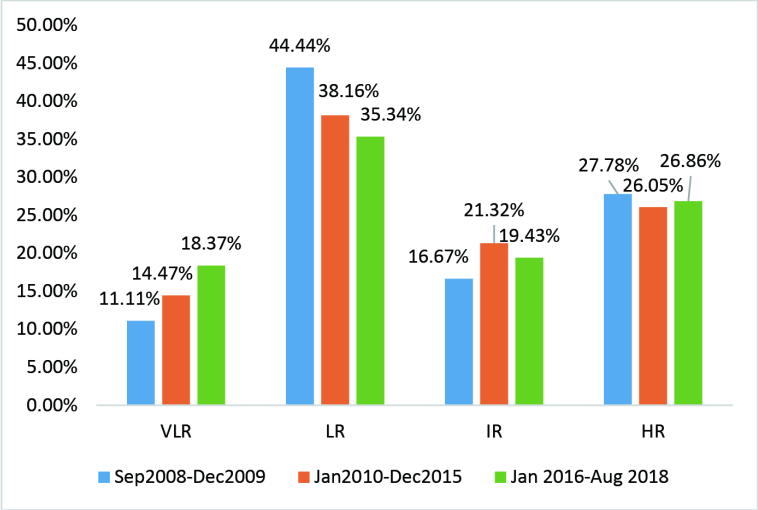

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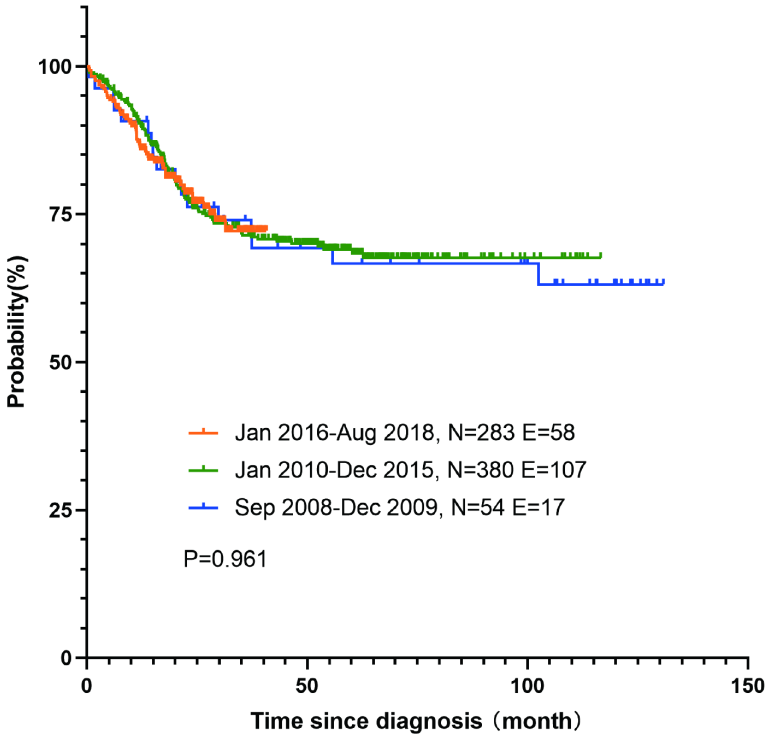

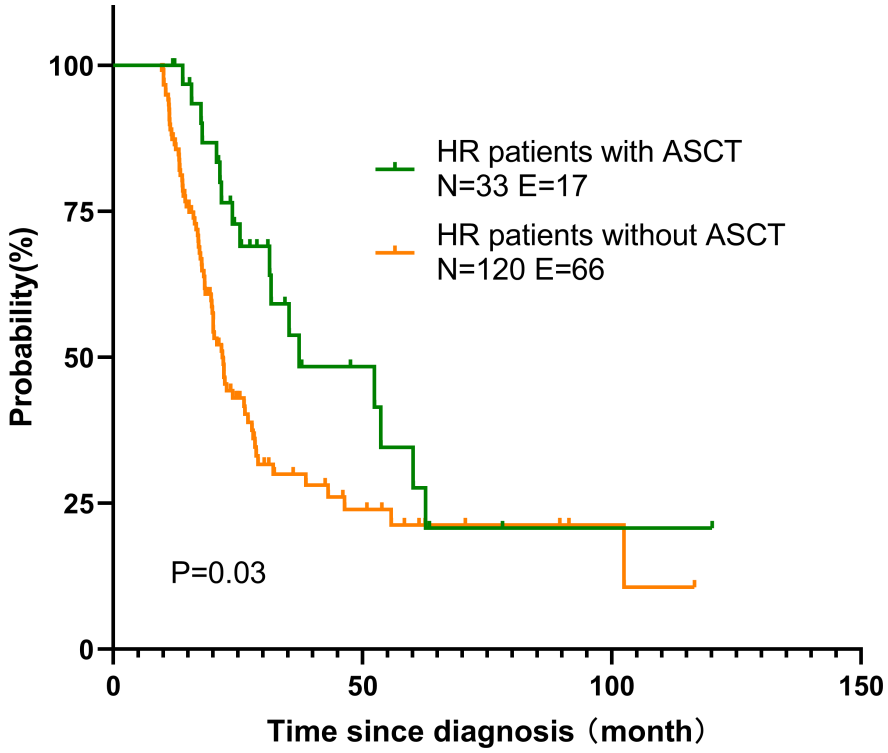

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