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Retrospective analysis of relapsed abdominal high-risk neuroblastoma

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ABSTRACT

Background/purpose: The impact of abdominal topography and surgical technique on resectability and local relapse pattern of relapsed abdominal high-risk neuroblastoma (R-HR-NB) is not clearly defined.
Methods: A sample of thirty-nine patients with R-HR-NB enrolled in the German neuroblastoma trials between 2001 and 2010 was analyzed retrospectively using surgical and imaging reports. We evaluated resectability and local relapse pattern within 6 standardized abdominal regions, impact of extent of the first resective surgery on overall survival (OS), and of number of operations and a higher cumulative surgical assessment score (C-SAS) on OS after the first event.
Results: In the left upper abdomen, rates for tumor persistence and relapse were 45.9% and 13.5% and in the left lower abdomen 27.7% and 8.3%, respectively. OS in months did not differ between complete and incomplete first resections (median (interquartile range): 35 (45.6) vs. 40 (65.4), $P = .649$). Better OS after the first event was associated with repeated as compared to single surgery (47.7 (64.7) vs. 4.3 (12.5), $P = .000$), and with higher as compared to lower C-SAS (47.7 (64.3) vs. 7.6 (14.7), $P = .002$).
Conclusions: OS after relapse/progression was not dependent on the extent of first resection. The number of operations was associated with better outcome after event.
Type of study: Treatment study.
Level of evidence: LEVEL III Retrospective comparative study.

The impact of surgery on overall survival (OS) of high-risk neuroblastoma is still subject of debate. While some publications did not find a benefit of complete resection during first-line treatment [1–3], others demonstrated survival benefit after complete resection [4–8]. Most studies focus on one surgical procedure [1,2,6,8] and there are still limited data on the value of repeated surgery. Moreover, most studies focus on the surgeon's report on the extent of surgery for categorization whether complete, gross total, or limited resection was performed [2,4,9]. Systematic data analysis of topography of operation, surgical access, extent of abdominal tumor burden, resectability, and relapse pattern after the first event is still missing for patients with abdominal high-risk neuroblastoma. It is not clear to what extent such data can be extracted sufficiently by the retrospective analysis of operative and imaging reports. However, such information is highly relevant for the pediatric surgeon and oncologist who need to decide whether to aim for complete resection during long operations with increased risk of complications or not in patients facing poor prognosis.

Our first aim was to analyze how often specific data on tumor resectability and relapse pattern in the abdomen could be retrieved retrospectively from written operative and imaging reports. More specifically, we investigated how high was the rate of incomplete resections and relapses in the anatomically challenging upper left abdominal region. Therefore, we did focus on the abdominal topographic relapse pattern using standardized abdominal topographic regions [10,11].

The second aim was to analyze what was the impact of extent of initial surgery, repeated surgery and the extent of repeated surgery on the outcome of high-risk neuroblastoma patients with persistence or relapse of abdominal tumors.

For this purpose, the correlation of surgical exposure, extent of resection and repeated surgery on overall survival and overall survival

Abbreviations: IOQ, Interquartile range; OS, overall survival; IVC, inferior vena cava; S1, first abdominal resecting surgery; S2, second abdominal resecting surgery; S3, third abdominal resecting surgery; OS, overall survival; SAS, surgical assessment score; C-SAS, cumulative surgical assessment score; LU, left upper abdominal region; LL, left lower abdominal region; RU, right upper abdominal region; RL, right lower abdominal region; IAU, upper interaortocaval region; IAL, lower interaortocaval region; +, Patient deceased; MEGA, myeloablative chemotherapy at start of consolidation therapy; RA, retinoic acid; MIBG, MIBG therapy; RT, external beam radiotherapy; AB, neuroblastoma anti-GD2 antibody therapy; TCE, topotecan, cyclophosphamide, etoposide; HR, hazard ratio; 95%-CI, 95% confidence interval.

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after the first event was evaluated both by a surgical assessment score (SAS) and by the sum of SAS, represented in a cumulative SAS (C-SAS). Specifically, the extent of bilateral colon mobilization was analyzed for tumors beyond midline.

The third aim was to evaluate if the impact of the extent of first surgery, number of surgical procedures and extent of repeated surgery on outcome was influenced by the following possible confounders: age at diagnosis, MYCN amplification, number of affected abdominal regions by the tumor at first event, histology, incidence of osteomedullar metastasis, use of the following therapy modalities after the first event: radiotherapy, MIBG therapy, number of chemotherapy cycles.

Our initial hypothesis was that information on topographic resectability and relapse pattern could be retrieved in the majority of cases from retrospective reports. In addition, our hypothesis was that repeated surgery and the extent of repeated surgery had a more pronounced impact on outcome as the extent of initial surgery and that this effect was robust against the possible confounders.

1. Methods

1.1. Patients

A sample of 39 patients from the German prospective neuroblastoma trials NB97 and NB2004 were included, when they met all following inclusion criteria: (1) INSS stage 4 abdominal neuroblastoma diagnosed according to international accepted criteria [12], (2) diagnosis between 2001 and 2010, (3) relapse or progression of locoregional abdominal neuroblastoma, (4) available imaging data in addition to the written records, (5) progression free interval of 120 days after first diagnosis in order to exclude patients with early progression during first-line induction chemotherapy who had no chance of second surgery, (6) at least one resective abdominal surgical procedure, and (7) guardian informed consent for data collection and treatment available.

Written records of 198 patients with abdominal high-risk neuroblastoma, initial diagnosis more than 5 years before study end and relapse after at least one abdominal resective surgery were available in the archive. Our intent for this study was to analyze if archived written surgical records yield sufficient information to determine the topographic regions affected by tumor and to analyze if the designed surgical score had any association with survival after surgery. We included 39 patients for whom imaging data were available in addition to the written records.

The trial protocols had been approved by the Institutional Ethical Boards of the University of Cologne and participating hospitals. All patients participated in the trial after informed consent and on voluntary basis. Trial protocol of the NB97 study and results of the primary trial end point have been published elsewhere [13]. According to the NB97 and NB2004 trial protocols, complete resection was advised when no vascular structures or adjacent organs were involved. Incomplete resection was acceptable to reduce the risk of acute complications and long-term organ impairments. Nephrectomy or insertion of vascular prostheses was discouraged. Patients without well-encapsulated primary tumors were recommended to undergo a first resective surgery after four to six cycles of induction chemotherapy [2]. In case an initial tumor biopsy was performed, the subsequent resection was referred to as second look surgery.

The study protocol required a tumor biopsy for histology and assessment of the status of oncogene MYCN and chromosome 1p unless >60% bone marrow assessment did allow molecular analysis using infiltrated bone marrow samples. The standard chemotherapy arm consisted of three cycles of cisplatin, etoposide, and vindesine, alternating with three cycles of vincristine, dacarbazine, ifosfamide, and doxorubicin. Patients were randomized to receive two additional cycles of topotecan, cyclophosphamide, and etoposide (TCE) before the standard chemotherapy. All 39 patients included in our study had no progression under induction chemotherapy.

An abdominal resective surgical procedure was usually scheduled after induction chemotherapy. Systematic sampling of regional lymph nodes was recommended by the trial protocol.

131I-MIBG-therapy with external beam irradiation boost was scheduled for a residual active primary in MIBG up taking residuals after this resecting surgery. Subsequently, consolidation therapy started with a myeloablative chemotherapy with melphalan, carboplatin, etoposide and autologous stem cell rescue, followed by nine cycles of oral retinoic acid.

For this analysis, operation notes, pathology reports, and postoperative imaging reports were reviewed by two independent experienced board-certified pediatric surgeons, and discrepant results were clarified after repeated joint review of the patients' files.

Only surgical procedures performed with intention to resect the tumor were included. Initial surgery for biopsy only was excluded.

1.2. Time points of assessment

Assessment of abdominal tumor was performed at initial diagnosis, at first resecting surgery (S1), at first staging after S1, at first event and, if performed, at 2nd (S2), or 3rd (S3) abdominal resecting surgery. Final assessment was carried out at last follow-up.

1.3. Definition of anatomical regions

For analysis of the extent and locoregional tumor growth pattern as well as the surgical approach to the tumor during operation, the abdomen was divided into six anatomical regions limited by aorta, respectively inferior vena cava (IVC), interaortocaval, and above or below the height of the renal vein as previously described by Tsuchida et al. [11]. Tumor on or behind the renal vessels was counted in both neighboring upper and lower regions. It was noted in how many patients the fate of tumor could be tracked retrospectively from written reports on initial imaging, postoperative imaging and imaging at first event.

1.4. Surgical access

For each region, we evaluated whether recommended standard surgical access procedures were performed [14]:

1.5. Upper regions

For abdominal neuroblastoma in the upper regions a transverse laparotomy is recommended. Additional incision of the diaphragm via abdominal or thoracic access should be considered in case of thoracoabdominal tumors.

For the right upper region, access includes right colon and duodenum mobilization, eventually with right-sided medial visceral rotation, according to Cattell–Braasch [15]. In addition, mobilization of the liver via incision of the right hepatic coronary ligament is a decisive maneuver for tumor in the most upper part of the retroperitoneum or diaphragm [16].

For the left upper region, applicable procedures are left colon and hepatic coronary ligament mobilization, opening through the lesser sac, and pancreas/spleen mobilization (left-sided medial visceral rotation, according to Mattox) [17].

1.6. Interaortocaval regions

For large tumor burden in the interaortocaval regions, bilateral colon mobilization from the left and the right side, as well as access to bursa omentalis, and pancreas/spleen mobilization should be considered (right-sided and left-sided medial visceral rotation).