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The results of concentration of care: Surgical outcomes of neuroblastoma in the Netherlands

Alida F.W. van der Steeg [a, b, *], Merel Jans [a], Godelieve Tytgat [a], Marta F. Fiocco [a, c, d], Cornelis van de Ven [a, e], Cecilia E.J. Terwisscha van Scheltinga [a, e], Rob Pieters [a], Max M. van Noesel [a, f], Anton H. van Dijk [g], Caroline C.C. Hulsker [a, h], Marc H.W.A. Wijnen [a, i]

[a] Princess Máxima Center for Pediatric Oncology, Heidelberglaan 25 3584, CS, Utrecht, the Netherlands
[b] Pediatric Surgical Center Amsterdam, Amsterdam University Medical Center, Meibergdreef 9, 1105, AZ, Amsterdam, the Netherlands
[c] Mathematical Institute, Leiden University, Niels Bohrweg 1, 2333, CA, Leiden, the Netherlands
[d] Department of Biomedical Data Science, Section Medical Statistics, Leiden University Medical Center, Albinusdreef 2, 2333, ZA, Leiden, the Netherlands
[e] Department of Pediatric Surgery, Sophia Children's Hospital, Erasmus Medical Center, Wytemaweg 80, 3015, CN, Rotterdam, the Netherlands
[f] Division Imaging & Cancer, Academic Medical Center Utrecht, Heidelberglaan 100, 3584, CX, Utrecht, the Netherlands
[g] Department of Pediatric Surgery, Beatrix Children's Hospital, Hanzeplein 1, 9713, GZ, Groningen, the Netherlands
[h] Department of Pediatric Surgery, Wilhelmina Children's Hospital, Lundlaan 6, 3584, EA, Utrecht, the Netherlands
[i] Department of Pediatric Surgery, Amalia Children's Hospital, Radboud Medical Center, Geert Grooteplein Zuid 32, 6525, GA, Nijmegen, the Netherlands

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ABSTRACT

Introduction.

In the Netherlands pediatric oncological care for solid tumours is concentrated in one centre since November 2014. One of the most frequently diagnosed solid non-brain tumours in children is the neuroblastoma. Results of surgical treatment of neuroblastoma since the start of this centralization are presented and compared to a historic cohort.

Methods.

The new national cohort of neuroblastoma (n = 111) consists of all consecutive patients treated between January 1st, 2015 and April 1st, 2021. The historic neuroblastoma cohort consists of all operated neuroblastoma patients in the Netherlands between 1998 and 2014 (n = 244). Intra-operative complications and surgical outcome were registered. Post-operative complications were divided in short (<30 days after surgery) and long term (>30 days). The severity of complications was graded using the Clavien Dindo Classification (CDC) system.

Results.

Intraoperative outcomes showed significant differences in favour of the new cohort with less blood loss ($p < 0.001$), fewer vascular complications ($p < 0.001$) and shorter duration of surgery ($p < 0.001$). Short term complications were comparable in numbers, but significantly more patients had CDC grade 3/4/5 complications in the historic cohort ($p = 0.005$). Long term complications did not differ.

Estimated overall survival showed a better survival in the new cohort (log rank 0.022).

Conclusion.

Centralization of care for neuroblastoma patients has led to a significant improvement of both intraoperative outcomes and short term complications.

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1. Introduction

Pediatric surgical oncology is one of the medical disciplines with limited patient numbers. The most frequent extra-cranial solid tumour in children is neuroblastoma.

* Corresponding author. Princess Máxima Center for Pediatric Oncology, Heidelberglaan 25 3584, CS, Utrecht, the Netherlands.
E-mail address: a.f.w.vandersteeg@prinsesmaximacentrum.nl (A.F.W. van der Steeg).

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Neuroblastoma has an annual incidence of 9.1 per million children under 18 years of age [1]. Overall survival is good in low-risk disease, however high-risk patients still have a poor 5-year overall survival of less than 50%, despite intensive multimodal treatment [1]. Surgical resection of the primary tumour is standard of care for most stages of disease.

Until recently, surgery for neuroblastoma in the Netherlands was performed by pediatric surgeons in 5 different academic centres, as part of the standard treatment. This means that with an annual incidence of about 25 newly diagnosed neuroblastoma cases 3–6 surgeries were performed per centre per year.

In recent years centralization of patients/diagnoses has become a major topic, although first reports concerning centralization date back to 1979 [2]. The general idea is that concentration of care leads to higher exposure of professionals to certain diagnoses, associated treatment and related complications, and thus should improve outcome for the patients. The first studies on concentration of (oncological) surgery in adults focused on the relationship between mortality and volume per hospital. These studies showed that there was a clear inverse relationship between mortality and hospital volume for complicated surgical procedures [2,3]. From focusing on hospital volume research interest shifted to surgeon volume and showed the influence of the experience of the surgeon being a major contributor to mortality [4]. Even in high-volume hospitals low-volume surgeons did worse than high-volume surgeons [5]. Further research showed that not only mortality was influenced by the volume of hospitals and surgeons, but also the incidence of complications decreased significantly when patients were treated by high-volume surgeons in high-volume hospitals [6]. The volume which was considered high-volume differed per surgical procedure and was based on the criteria of the Leapfrog group in the USA, which is a non-profit organization that serves as a voice for healthcare consumers by using hospital surveys [7]. The Leapfrog Group has set volume standards for 10 complex surgical procedures. For pediatric oncological surgery no standards are formulated, but for adult surgical procedures such as esophagectomy performing ten procedures annually is considered high-volume. The benefit of concentration for surgical outcomes has been proven for several diagnoses in adults [8–10]. Concerning pediatric surgery some international initiatives have been undertaken to centralize for example biliary atresia [11] and oesophageal atresia [12]. However, so far centralization is not mandatory. In the Netherlands, initiatives to centralize general pediatric surgery have started but have so far not led to a significant change in organization of care [13].

All pediatric oncological diagnoses can be classified as rare diseases and centralized care for patients suffering from pediatric malignancies has been shown to enhance cure rates [14]. In the Netherlands this has led to an initiative by oncologists and parents of children with cancer to centralize pediatric oncological care in one national centre, the Princess Máxima Center for Pediatric Oncology. This centre opened its doors for all patients with extra-cranial solid tumours in the Netherlands from November 2014 onwards and for all childhood cancer patients in May 2018.

In this study we present the results of the surgical treatment of neuroblastoma patients since the start of concentration and compare the results to a historic cohort. We hypothesized that the intraoperative outcomes such as blood loss and operating time would have improved and that the incidence of post-operative complications such as fever, intussusception, and diarrhoea would be lower in the new cohort.

2. Methods

2.1. Patients

2.1.1. Historic cohort 1998–2014

This is a retrospective multicentre cohort. All patients with (ganglio)neuroblastoma who underwent resection of their primary tumour by pediatric surgeons between January 1998 and the end of 2014 in the Netherlands were included. Their medical files were reviewed for intra- and postoperative complications. Exclusion criteria were: surgery performed abroad or by surgeons other than members of the pediatric surgical team such as neuro-surgeons (usually dumbbell neuroblastomas) or head-and-neck surgeons (for neuroblastomas located cervically).

This retrospective study was approved by the Medical Research Ethics Committee (MREC) of the University of Utrecht Medical Center, Utrecht, The Netherlands (reference number 15–709/C) and the requirement of separate informed consent was waived.

2.1.2. New cohort 2015–2021

All patients with newly diagnosed neuroblastoma who underwent surgery in the Princess Máxima Center between January 1st, 2015 and April 1st, 2021 were included. In 2015 one patient received surgery in another clinic. This patient was left out of the analyses. Patients were treated according to the SIOPEN protocol. Data recovered from the electronic patient file included: age at diagnosis, gender, age at surgery, complications intraoperatively, post-operatively within the first 30 days and post-operatively long term. Complications in the new cohort were registered during hospital admittance, and during follow-up at the outpatient clinic and at the long term follow-up clinic for late effects of treatment. All post-operative complications were graded using the Clavien-Dindo classification [15].

2.2. Surgery

Only the neuroblastoma patients who underwent surgery were included in the study. In the new cohort patients with stage 4s were not operated, but treated with watchful waiting or chemotherapy only. When the tumour progressed to stage 4 surgery was indicated. In the new cohort surgery was deemed possible if the SIOPEN score on the MIBG scan [16] was 3 or less after neo-adjuvant treatment.

2.3. Definition of complications

Before data collection in the historic and new cohort complications to be recorded were clearly defined (Table 1). As basis for the definitions we used the registration system of complications proposed by the Netherlands Association of Surgeons [17]. The definitions of complications registered were determined beforehand for the new cohort. Short term complications were registered both during post-operative admission and in the outpatient clinic. Long term complications were registered during the oncological follow-up in the first 5 years after diagnosis and in the standardized follow up protocol in which all childhood cancer survivors in the Netherlands can participate. Only surgical complications were registered. Complications due to toxicity of either chemotherapy, radiotherapy or immunotherapy were not taken into account.

2.3.1. Intraoperatively

Duration of surgery: Moment of first incision until completion of last skin suture. The length was measured in minutes.

Blood loss: measured in ml. The amount of blood loss was either deduced from the surgical notes or in case this was not provided

Table 1
Definitions of short- and long term surgical complications.

Short term complications (within 30 days)	
Chylous ascites	ascites requiring drainage, enteral diet and/or total parental feeding
Diarrhoea	duration of 7 days or more, or inducing electrolyte disturbances that needed treatment
Gastroparesis	Requiring duodenal feeding tube or total parental feeding
Fever	Prescription of antibiotics necessary; defined cause not required
Anaemia	requiring blood transfusion more than 24 h after surgery; blood transfusions during or immediately after surgery were excluded
Pediatric intensive care unit (PICU) admittance	Longer than 24 h post-surgery of re-admission
Post-operative pain	Requiring an intervention under general anaesthesia such as placement of a (new) epidural catheter.
Pneumonia	Diagnosed with chest X-ray or CT-scan
Urinary tract infection	Positive urine culture
Second and consecutive surgery	Either planned during surgery (e.g. major blood loss during tumour resection requiring packing) or unplanned procedures under general anaesthesia
Mortality	Within 30 days after surgery due to surgical complications
Long term complications (> 30 days after surgery)	
Kidney failure[a]	Requiring dialysis
Vanishing kidney	Kidey atrophy due to vascular damage as a result of surgery
Second surgery	In case of bowel obstruction due to adhesions or incisional hernia
Prolonged diarrhoea	Requiring supplemental electrolytes

[a] as defined by the kidney disease improving global outcomes (KDIGO) consensus conference [18].

the anaesthesiologist report was consulted. When data on blood loss were not available this was classified as unknown. For each patient, blood loss was then compared to the total blood volume (TBV) of the patient (weight of patient in kg times 80 ml) to calculate the blood loss as percentage of the TBV. Major haemorrhage was defined as more than 30% TBV loss.

Unplanned nephrectomy: when the surgical report did not mention the nephrectomy was pre-operatively planned due to either involvement of the kidney or vascular pedicle in the tumour or a pre-existent renal problem such as cystic kidney disease.

Major vascular complications: serious injury to the central vessels (i.e. aorta, vena cava, celiac axis, superior mesenteric artery, portal vein) either leading to major blood loss (i.e. > 30% of total blood volume) or serious sequelae such as bowel ischemia or necessity of vascular prosthesis.

2.4. Clavien Dindo Classification

For both short and long term complications the Clavien Dindo Classification (CDC) system was used to assess the impact of the complication (see Supplemental Table 2). In case of multiple complications only the highest score was noted.

2.5. Statistical analyses

Categorical variables are presented as numbers with percentages. Differences between the cohorts were tested using χ^2. CDC grades were grouped in 1/2 and 3/4/5. Grade 1/2 are complications that either require no treatment or require medication without detrimental effects for the patient. Grades 3/4/5 are those complications that need invasive treatment (for instance relaparotomy or drain placement) or admission to the Intensive Care Unit and tend to have more negative effects on recovery. Continuous variables are shown as median (IQR) with differences assessed using Mann-Whitney *U* test. $P < 0.05$ was considered to be statistically significant. All analyses were performed using SPSS software version 26.

3. Results

The historic cohort contained 292 patients and the new cohort contained 122 patients. There were no significant differences in basic characteristics, with the exception of age at diagnosis (Table 2). Considering the patient numbers per anatomical site, we focused further analyses only on the patients that received abdominal surgery or a thoraco-phrenico-laparotomy. This included 244 for the historic cohort and 111 patients in the new cohort.

In the historic cohort surgery was performed by over 40 surgeons and numbers per hospital per year ranged from less than one to eight per year. In the new cohort, surgeries were performed in one center by teams of 2 surgeons with a total number of five surgeons of whom two were also involved in the historic cohort and numbers ranged from 10 to 24 per year (suppl Table 1).

3.1. Intraoperative complications

The surgical outcome parameters duration of surgery, blood loss, unplanned nephrectomy, and major vascular complications showed a significant difference in favour of the new cohort (Table 3). Length of surgery diminished with 40% from 275 to 168 min ($p < 0.001$) and blood loss was reduced with 90% from 450 to 50 ml ($p < 0.001$).

In 8/244 patients of the historic cohort a nephrectomy was planned beforehand either because of a non-functioning kidney (e.g. pre-existent cystic kidney) or because of involvement of the vascular pedicle of the kidney. In the new cohort there were no planned nephrectomies. In 11/236 patients a nephrectomy was performed unplanned in the historic cohort versus 2/111 in the new cohort ($p = 0.021$). Major vascular complications such as significant damage of the aorta which required a vascular prosthesis or unintentional ligation of the mesenteric superior artery were more frequent in the historic cohort (64/244 vs 5/111) ($p < 0.001$). Image-Defined Risk Factors (IDRFs) were more frequent in the new cohort ($p = 0.007$). The incidence of major haemorrhage and major vascular complications in patients with IDRFs was significantly lower in the new cohort compared to the historic cohort (Table 3).

3.2. Complications

The percentage of patients with complications during the first 30 days after surgery did not differ between the two cohorts. The clinical impact of the complications according to the Clavien Dindo classification (CDC) was different between the cohorts. In the historic cohort significantly more grade 3/4/5 complications were

Table 2
Basic characteristics patients.

		Historic cohort	New cohort	p-value
Age in months at diagnosis (median, IQR)		24.5 (10.0–46.0)	30.5 (15.8–52.0)	0.015
Gender Male (%)		138 (56.6)	65 (58.6)	0.730
Localization primary tumour (%)		N = 292 (100)	N = 122 (100)	0.094
	Cervical	4 (1.4)	3 (2.5)	
	Thorax	33 (11.3)	5 (4.1)	
	Thorax + abdomen	17 (5.8)	3 (2.5)	
	Abdomen	227 (77.7)	108 (88.5)	
	Pelvic	10 (3.4)	3 (2.5)	
	Multifocal	1 (0.3)	0	
Stage Abdominal Tumours (%)		N = 244 (100)	N = 111 (100)	0.591
Stage I		24 (9.8)	6 (5.4)	
Stage II		15 (6.2)	6 (5.4)	
Stage III		39 (16)	19 (17.1)	
Stage IV		161 (66)	79 (71.2)	
Stage IVs		5 (2.0)	1 (0.9)	

Table 3
Intraoperative features and complications.

	Historic cohort n = 244	New cohort n = 111	p-value
Age at surgery in months (median; IQR)	30.0 (14.0–51.0)	35.0 (24.0–59.0)	0.056
Duration of surgery in minutes(IQR)	275 (212.5–381.3)	168 (116–227)	<0.001
Blood loss in ml (IQR)	450 (157.5–1013.8)	50 (10–130)	<0.001
None (%)	17 (7.6)	25 (22.7)	<0.001
<10% of TBV (%)	43 (17.8)	54 (49.1)	
10–19% of TBV (%)	23 (9.5)	24 (21.8)	
20–29% of TBV (%)	12 (5.0)	4 (3.6)	
>30% of TBV(%)	75 (31.1)	2 (1.8)	
Unknown (%)	71 (29.5)	1 (0.9)	
Nephrectomy	19 (8.2)	2 (1.8)	0.021
unplanned	11	2	
Major vascular complications	64 (26.2)	5 (4.5)	<0.001
Image defined risk factors (IDRF) (%)_	130 (53.3)	78 (70.3)	0.007
IDRF and major haemorrhage	57/127 (43.8)	2/78 (2.6)	<0.001
IDRF and major vascular complication	47/130 (36.2)	5/78 (6.4)	<0.001
Per-operative mortality	1 (0.4)	0	0.499

observed compared to the new cohort (p = 0.005; Table 4). Reason for CDC 4 in all patients was ICU (re)admittance for different reasons. The most frequent noted complications are shown in Table 4 with their CDC grade.

The long-term complications did not significantly differ between the two cohorts (11.8% vs 9.0%; Table 4). Local relapse numbers showed no significant difference between both groups (13.4% versus 8.2%; Table 4). The most frequent long term complications in both cohorts were the ileus due to bowel obstruction requiring surgery and the vanishing kidney.

Concerning EFS overall (Fig. 1) and relapse only (Fig. 2) the Kaplan Meier curves showed no significant differences (logrank 0.260 and 0.252 respectively) between the two cohorts. OS was significantly better in the new cohort (Fig. 3; logrank 0.022).

4. Discussion

In this study we tried to analyse the effect of concentration of (surgical) care on intraoperative, short -, and long term complication rates in resections of neuroblastoma.

Results show that the concentration of pediatric oncological surgical care in the Netherlands has led to a decrease in intra- and post-operative complications in neuroblastoma surgery. The variation in intraoperative parameters decreased significantly with shorter surgical time, less blood loss and fewer vascular complications. One might argue that shorter surgical time and less blood loss may imply less complete resections, however the incidence of (local) relapses was comparable for both cohorts. Another factor that may influence the surgical outcomes is the presence of Image Defined Risk Factors (IRDFs). They form the base for the classification of neuroblastoma patients and were defined in 2011 by Brisse et al. [19] Before 2011 these risk factors such as encasement of central vessels and involvement of intra-abdominal organs were denominated surgical risk factors and were shown to have significant impact on surgical outcomes [20–22]. In our study IDRFs were more frequent in the new cohort but surgical outcomes were better.

The extent of surgery, the risks undertaken to achieve a complete resection and the effect of radiotherapy in neuroblastoma patients have been a matter of debate for many years. The extent of resection of the primary tumour and local lymph node metastases is an important component of treatment, however the specific impact on local recurrence, EFS and OS remains unclear [23,24]. Von Almen et al. showed a significantly better EFS with a resection of >90% of the neuroblastoma, however influence on OS was not clear [25]. More recently, Holmes et al. showed an improved EFS and OS after complete macroscopic excision compared to incomplete excision (defined as visible tumor tissue left behind, not further quantified). Associated factors with an incomplete excision in this paper were centrally located abdominal tumor and the presence of IDRFs [26]. With these conflicting results the question remains how much risk has to be undertaken to achieve a complete macroscopic excision of the primary tumour. One of the topics within this discussion is the nephrectomy. In our historic cohort the percentage of nephrectomies, both planned and inadvertent was significantly higher compared to the new cohort. In addition there

Table 4
Short term (<30 days post-surgery) and long term complications.

	Historic cohort (n = 244)	New cohort (n = 111)	p-value	
Short term complications Yes (%)	104 (43.1)	41 (36.9)	0.538	
Number of complications per patient (%)	N = 104	N = 41		
1	68 (27.8)	30 (27.0)		
2	21 (8.6)	8 (7.2)		
3	11 (4.5)	3 (2.7)		
4	4 (1.6)	0		
Clavien-Dindo classification (%)				
Grade 1	19 (7.8)	7 (6.3)		
Grade 2	47 (19.3)	28 (25.2)		
Grade 3	10 (4.1)	5 (4.5)		
Grade 4	25 (10.2)	1 (0.9)		
Grade 5	4 (1.6)	0		
Grade 1/2	66 (27.0)	35 (31.5)	0.386	
Grade 3/4/5	39 (16.0)	6 (5.4)	0.005	
Most frequent complications (%)				
Fever (CDC 2)	22 (9.0)	16 (14.4)		
Electrolyte disturbances (CDC 1)	18 (7.3)	1 (0.9)		
Diarrhoea (CDC 1 or 2)	7 (2.8)	2 (1.8)		
Paralytic ileus (CDC 2)	7 (2.8)	0		
Gastroparesis (CDC 2)	3 (1.2)	8 (7.2)		
Follow up (months; IQR)	39 (13–83)	24 (12–46)		<0.001
Long term complications Yes (%)	28 (11.8)	10 (9.0)		0.259
Clavien-Dindo classification (%)				
Grade 1	15 (6.1)	1 (0.9)		
Grade 2	5 (2.0)	5 (4.5)		
Grade 3	8 (3.3)	3 (2.7)		
Grade 4	0	1 (0.9)		
Grade 5	0	1 (0.9)		
Grade 1/2	20 (8.2)	6 (5.4)		0.349
Grade 3/4/5	8 (3.3)	5 (4.5)		0.569
Local relapse (%)	34 (13.9)	10 (9)		0.192
Most frequent complications (%)				
Vanishing kidney (CDC 1)	10 (4.1)	1 (0.9)		
Ileus due to bowel obstruction(CDC 3)	5 (2)	2 (1.8)		

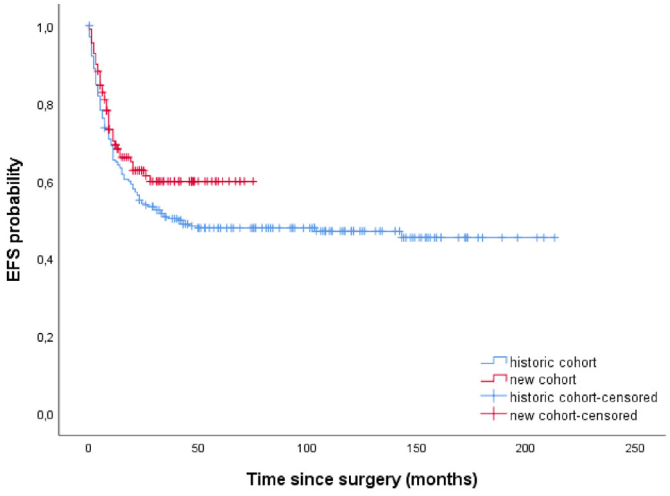

Fig. 1. Estimated EFS for neuroblastoma provided by Kaplan Meier's methodology (log rank 0.260).

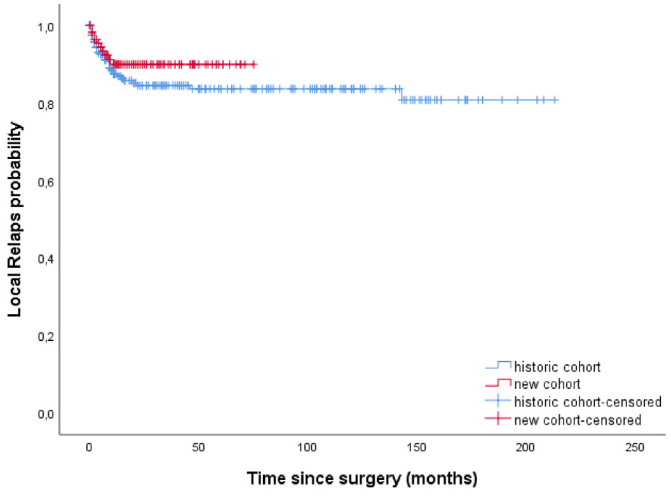

Fig. 2. Estimated local relapse for neuroblastoma provided by Kaplan Meier's methodology (log rank 0.252).

were 10 vanishing kidneys reported in the long term complication registry. A vanishing kidney is caused by hypoperfusion of the kidney due to (unrecognized) vascular injury and can be considered as a functional nephrectomy. The fact that next to the nephrectomies there was a substantial number of vanishing kidneys may be an indication of the risks accepted to achieve a complete macroscopic excision. However, the long-term sequelae of losing a kidney should not be overlooked and may result in renal dysfunction, proteinuria, and hypertension. A study by Knijnenbrug et al. in a Dutch childhood cancer survivor cohort showed that 28.1% of all survivors had at least one renal adverse event at a median age of 19.3 years. Survivors who had undergone a nephrectomy had the highest risk for diminished renal function (odds ratio 8.6) [27]. Other international studies showed that, in addition to acute kidney injury, a nephrectomy was one of the most important risk-factors for late-onset kidney failure [28,29]. In our study, the children with a vanishing kidney or a nephrectomy did not show any clinical signs of chronic kidney disease at this point in time and

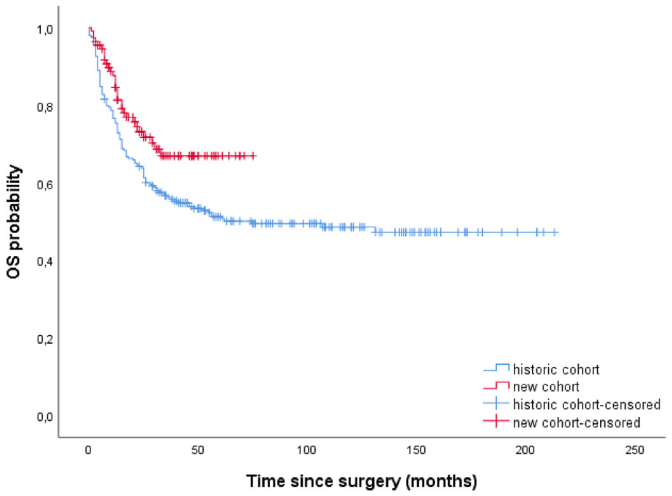

Fig. 3. Estimated OS for neuroblastoma provided by Kaplan Meier's methodology (log rank 0.022).

were in the CDC thus scored as a grade 1. However, this may underestimate the severity of their long-term sequelae.

In the new cohort the surgical strategy was to remove as much tumor as possible without damaging any organs or essential blood vessels. This difference in surgical approach is not reflected in the rate of local recurrence, which is comparable for both cohorts.

Concerning the complications, the short term complications were comparable in numbers but significantly less severe in the new cohort, whereas the long term complications were comparable in both numbers and severity.

Complications after surgery can be a major problem, leading to morbidity for the patient, longer hospital stay and higher costs. In addition, complications may have an impact on (event free) survival since they can lead to postponing adjuvant (high dose) chemotherapy [30]. However, comparing our results to existing literature concerning complications in neuroblastoma literature is difficult since the number of complications and their impact are often hard to discern from the present literature. The reasons for this are twofold: first clear definitions of complications are lacking and second a reliable registration system needs to be in place [22,31]. This is an important limitation of this study since a reliable system was only in place for the new cohort with continuous attention for the occurrence of complications and this may have influenced the number of complications registered, whereas the data accrual for the historic cohort was retrospective and completely dependent on the quality of the medical records at the time. In addition it is difficult to discern from the historic data whether possible complications were not mentioned because they were not diagnosed or whether they were not assessed. This may have led to underreporting of complications in the historical cohort.

Quality of life in adult oncology patients is significantly influenced by the occurrence of post-operative complications, especially severe complications [32]. In addition to quality of life, health status, anxiety and depressive feelings are also greatly influenced by complications that occur, and this influence is related to the severity of the complications as is shown in research in colorectal carcinoma patients [33]. It seems reasonable to assume that the same relationship is applicable to pediatric surgical patients, but this warrants further research.

5. Conclusion

The concentration of pediatric surgical care for neuroblastoma patients has led to significant improvements intra-operatively and post-operatively in the first 30 days. Longer follow-up is needed to establish a clear benefit on the late post-operative complications as well. In order to further improve the surgical outcomes it is important to maintain a sufficient registration system for per- and postoperative outcomes and – complications with clear definitions. The SIOPEN, COG and GPOH together have suggested a standard for systematic reporting of neuroblastoma surgery [34]. This is a good start but needs a commitment of all surgeons to register their patients and compare results.

Declaration of interest statement: none declared

Role of the funding source: the funding source had no influence on the data acquisition, no influence on the statistical analyses of the data, and no influence on the interpretation of the analyses.

CRediT authorship contribution statement

Alida FW. van der Steeg: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, writing – review & editing, Visualization. **Merel Jans:** Conceptualization, Methodology, Investigation, Writing – original draft, Project administration, Funding acquisition. **Godelieve Tytgat:** Conceptualization, Data curation, writing – review & editing, Supervision. **Marta F. Fiocco:** Methodology, Validation, Formal analysis, Investigation, writing – review & editing. **Cornelis van de Ven:** Conceptualization, Validation, Resources, Data curation, Writing – original draft. **CeciliaEJ. Terwisscha van Scheltinga:** Conceptualization, Resources, Data curation, writing – review & editing. **Rob Pieters:** Validation, Formal analysis, Writing – original draft, writing – review & editing, Max. **Max M. van Noesel:** Conceptualization, Resources, writing – review & editing. **Anton H. van Dijk:** Validation, Investigation, Resources, Data curation, writing – review & editing. **Caroline CC. Hulsker:** Investigation, Resources, Data curation, writing – review & editing. **Marc HWA. Wijnen:** Conceptualization, Investigation, Resources, Data curation, writing – review & editing, Supervision, Funding acquisition.

Conflict of interest statement

None of the authors have a conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2022.10.005.

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