



original reports

Influence of Surgical Excision on the Survival of Patients With Stage 4 High-Risk Neuroblastoma: A Report From the HR-NBL1/SIOPEN Study

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abstract

PURPOSE To evaluate the impact of surgeon-assessed extent of primary tumor resection on local progression and survival in patients in the International Society of Pediatric Oncology Europe Neuroblastoma Group High-Risk Neuroblastoma 1 trial.

PATIENTS AND METHODS Patients recruited between 2002 and 2015 with stage 4 disease > 1 year or stage 4/4S with *MYCN* amplification < 1 year who had completed induction without progression, achieved response criteria for high-dose therapy (HDT), and had no resection before induction were included. Data were collected on the extent of primary tumor excision, severe operative complications, and outcome.

RESULTS A total of 1,531 patients were included (median observation time, 6.1 years). Surgeon-assessed extent of resection included complete macroscopic excision (CME) in 1,172 patients (77%) and incomplete macroscopic resection (IME) in 359 (23%). Surgical mortality was 7 (0.46%) of 1,531. Severe operative complications occurred in 142 patients (9.7%), and nephrectomy was performed in 124 (8.8%). Five-year event-free survival (EFS) \pm SE (0.40 ± 0.01) and overall survival (OS; 0.45 ± 0.02) were significantly higher with CME compared with IME (5-year EFS, 0.33 ± 0.03 ; 5-year OS, 0.37 ± 0.03 ; $P < .001$ and $P = .004$). The cumulative incidence of local progression (CILP) was significantly lower after CME (0.17 ± 0.01) compared with IME (0.30 ± 0.02 ; $P < .001$). With immunotherapy, outcomes were still superior with CME versus IME (5-year EFS, 0.47 ± 0.02 v 0.39 ± 0.04 ; $P = .038$); CILP was 0.14 ± 0.01 after CME and 0.27 ± 0.03 after IME ($P < .002$). A hazard ratio of 1.3 for EFS associated with IME compared with CME was observed before and after the introduction of immunotherapy ($P = .030$ and $P = .038$).

CONCLUSION In patients with stage 4 high-risk neuroblastoma who have responded to induction therapy, CME of the primary tumor is associated with improved survival and local control after HDT, local radiotherapy (21 Gy), and immunotherapy.

J Clin Oncol 38:2902-2915. © 2020 by American Society of Clinical Oncology

INTRODUCTION

Despite recent therapeutic advances, many patients with high-risk neuroblastoma will not be long-term survivors¹⁻⁶; their outcome needs to be improved. The current therapeutic multimodality approach comprises induction chemotherapy; therapy to the site of the primary tumor (surgical excision and radiotherapy); high-dose therapy (HDT) with hematopoietic stem-cell rescue (SCR); and residual disease therapy, including immunotherapy.¹⁻⁶ To date, clinical trials have focused on induction, HDT, and immunotherapy,¹⁻⁷ with less attention directed to local therapy, and

there have been no randomized trials to examine the effect of the extent of excision of the primary tumor.

Although challenging and time consuming, complete macroscopic excision (CME) can be performed for the most extensive tumors with low morbidity and mortality.⁸ However, there are conflicting reports⁹⁻¹⁹ as to the benefit.

The primary aim of this analysis was to determine the relationship between the extent of surgeon-assessed primary tumor resection and event-free survival (EFS), overall survival (OS), and local progression (cumulative incidence of local progression [CILP]) of patients with

ASSOCIATED CONTENT

Data Supplement Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on May 15, 2020 and published at ascopubs.org/journal/jco on July 8, 2020; DOI <https://doi.org/10.1200/JCO.19.03117>

Written on behalf of the International Society of Paediatric Oncology Europe Neuroblastoma Group (SIOPEN).

CONTEXT

Key Objective

This study investigated the influence of surgical excision on the outcome of a large (1,531) cohort of patients, enrolled by 128 institutions in 18 countries, with high-risk neuroblastoma treated in the International Society of Pediatric Oncology Europe Neuroblastoma Group High Risk-Neuroblastoma 1 trial.

Knowledge Generated

In both the pre- and the postimmunotherapy eras, there was a higher overall and event-free survival and a lower cumulative incidence of local progression in patients with complete, compared with incomplete, macroscopic excision of the primary tumor. Furthermore, complete macroscopic excision was accompanied by low severe operative complication (9.7%) and mortality (0.46%) rates.

Relevance

In patients with high-risk neuroblastoma in the context of an intensive chemotherapy regimen followed by high-dose therapy, local radiotherapy (21 Gy), and immunotherapy, the goal of surgery should be complete surgical excision of the tumor.

stage 4 high-risk neuroblastoma who were treated in the International Society of Pediatric Oncology Europe Neuroblastoma Group High-Risk Neuroblastoma 1 (HR-NBL1/SIOPEN) trial.

PATIENTS AND METHODS

Patients included in this study were enrolled on the HR-NBL1/SIOPEN trial from June 2002 to December 2015 who fulfilled the eligibility criteria: stage 4 > 1 year or stage 4 or 4S with *MYCN* amplification < 1 year; completion of rapid COJEC (cisplatin, vincristine, carboplatin, etoposide, and cyclophosphamide)^{1,7,20} induction without progression; and no resection before induction, surgery, and achievement of the criteria for HDT¹ (complete bone marrow remission and at least a partial metastatic response at skeletal sites on ¹²³I-metaiodobenzylguanidine [MIBG] scintigraphy). If these criteria were not achieved, two courses of topotecan, vincristine, and doxorubicin (TVD)²¹ were given (Fig 1). No patients were given specific therapy for tumors with anaplastic lymphoma kinase aberrations.

In patients fulfilling the criteria for HDT, CME of the primary tumor was recommended. Postponement of operation until after HDT/SCR was permitted if the tumor was deemed unresectable. From June 2002 to October 2010, eligible patients were randomly assigned to receive busulfan and melphalan (BuMel) or carboplatin, etoposide, and melphalan as HDT.¹ After October 2010, in view of the results of randomization, all patients received BuMel.^{1,2}

After HDT/SCR, radiotherapy (21 Gy in 14 fractions over 18-20 days) was given to the preoperative volume of the primary tumor and involved regional lymph nodes regardless of the degree of surgical resection. No dose modification was used in the event of incomplete tumor excision, and metastatic sites were not irradiated. Omission of radiotherapy was discussed with the radiotherapy coordinators if

the primary tumor was considered unsuitable because of the site and the volume.

From June 2002 to September 2009, all patients were given isotretinoin orally after completion of radiotherapy. From October 2009 to August 2013, patients were randomly assigned to dinutuximab beta and isotretinoin or dinutuximab beta with subcutaneous interleukin 2 and isotretinoin.² From September 2013 to December 2015, patients received dinutuximab beta and isotretinoin.

The primary end points and description of the protocol have been published.^{1,2,20} Biologic features were determined in SIOPEN reference laboratories.^{22,23} Response to treatment was largely determined by computed tomography (CT) postcontrast enhanced scanning and assessed using International Neuroblastoma Response Criteria.²⁴

Parents/guardians and patients according to age provided written informed consent for treatment, data collection, and analysis. The trial was approved by national regulatory authorities and by national and institutional ethical committees and/or review boards.

Surgery

The protocol strongly encouraged CME of the primary tumor ideally before HDT. Removal of all visible and palpable tumor, including related involved lymph nodes, was defined as CME. When visible or palpable tumor remained after attempted excision, the procedure was defined as incomplete macroscopic excision (IME), irrespective of the volume of remaining tumor. If nephrectomy was deemed necessary to obtain CME, the operation could be postponed until after HDT to preserve renal function. Tumor resection was permitted at 1 of 3 time points: < 60 days after the end of induction (EOI), > 60 days after EOI following TVD, or after HDT.

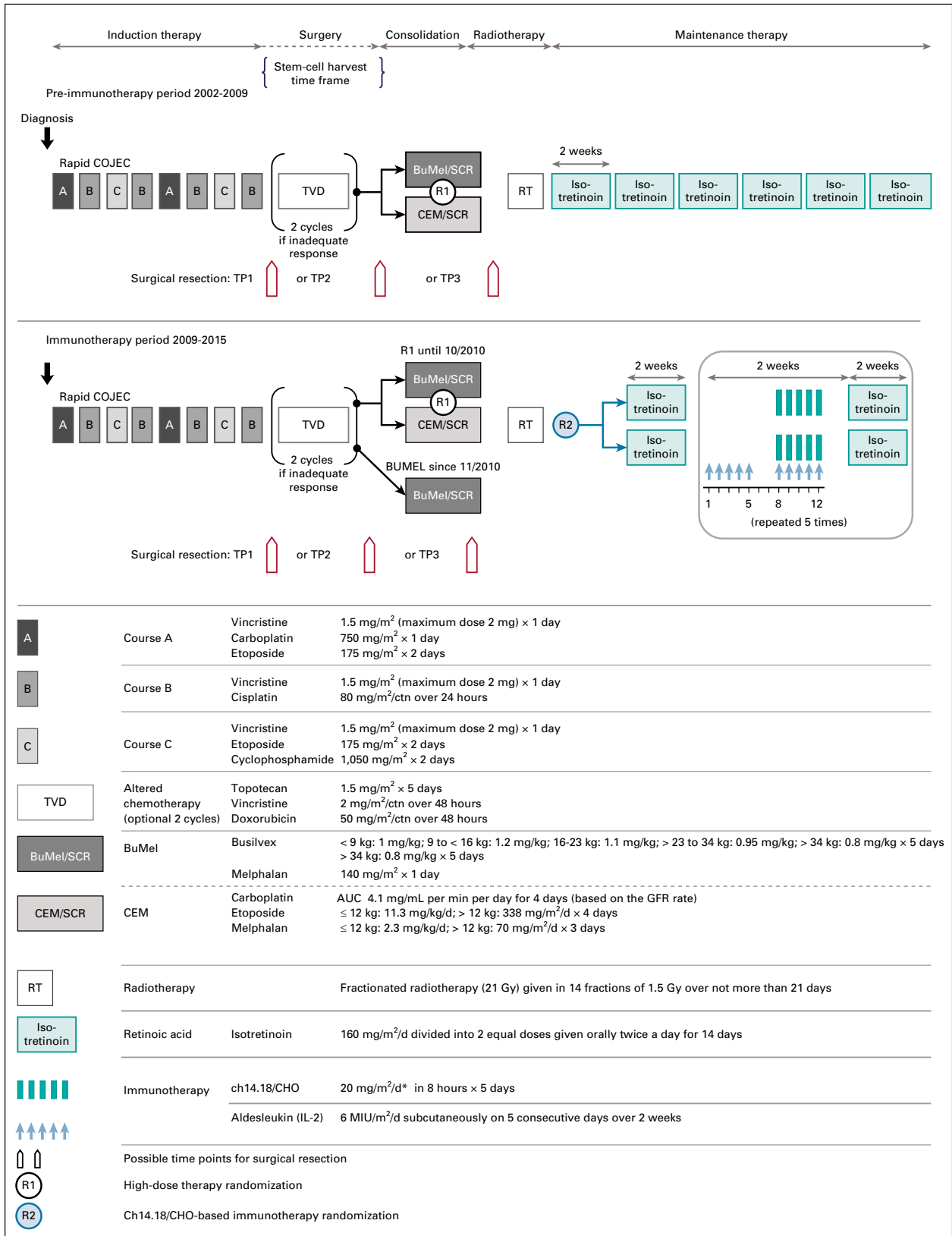


FIG 1. HR-NBL1/SIOPEN treatment overview. AUC, area under the concentration curve; ch14.18/CHO, dinutuximab beta; COJEC, cisplatin, vincristine, carboplatin, etoposide, and cyclophosphamide; ctn, continuous infusion; GFR, glomerular filtration rate; IL-2, interleukin 2; SCR, stem-cell rescue; TP, time point. (*) Infants and children with a body weight < 12 kg will be dosed at 0.67 mg/kg/d. In infants weighing ≤ 5 kg, an additional one-third dose reduction is advised.

Operations were performed in designated pediatric oncology centers by surgeons who were cognizant of the challenges and goals of the study. The feasibility of tumor excision was judged by multidisciplinary teams (pediatric surgeons, oncologists, radiologists, and radiation oncologists) at each treating institution. Because patients with high-risk neuroblastoma frequently exhibit preoperative image-defined risk factors (IDRFs²⁵⁻²⁸; previously termed surgical risk factors²⁵), even after induction, their presence was not considered a contraindication to operation.

The operation principles, as described by Kiely,²⁹ were to display natural anatomy by reflecting overlying viscera then dissecting along the plane of major blood vessels from areas free from tumor encasement toward the disease.

Operation-Related Data and Definitions

Data were collected on presence of IDRFs, completeness of tumor excision (determined by the surgical team at the conclusion of the operation), severe operative complications, nephrectomy, death within 30 days as a result of the operation or any cause, local progression or relapse, and a second neoplasm. Two-dimensional imaging (largely CT scanning) was used to identify IDRFs,²⁵⁻²⁸ which were deemed present if the tumor surrounded a vital structure, typically a major blood vessel.²⁷ Because the SIOPEN radiology committee did not consider the sensitivity of contemporary imaging reliable enough to distinguish the effects of operation, including edema and hematoma, from residual tumor, postoperative imaging was not routinely used. Hemorrhage > 30% of blood volume, vascular injury leading to loss of tissue, major ascites or pleural effusion, spinal cord injury, peripheral nerve injury leading to loss of function, and any organ failure were recorded as severe operative complications.

Statistical Analysis

Median follow-up time was calculated using the reverse Kaplan-Meier estimate.³⁰ The Kaplan-Meier method was used to estimate EFS and OS. EFS was defined as the time from diagnosis to the first occurrence of relapse, progression, secondary malignancy, or death; OS was defined as death as a result of any cause. Patients with no event were censored at the date of their last follow-up. For statistical comparisons, log-rank test and Cox regression³¹ were used for the entire cohort and separately for patients included from June 2002 to June 2009 and patients included from July 2009 to December 2015. CILP was estimated in consideration of local relapse, local progression, or death as a result of progression of the primary tumor as event and while taking into account the competing risk of isolated distant relapse, disease progression, and death as a result of causes other than relapse.³¹ The statistical comparison of cumulative incidences was done using Gray's test and the Fine and Gray model.³² Unless otherwise stated, data are given as mean \pm SE. EFS, OS, and CILP are presented as 3-year and 5-year point estimates with standard errors.

The number of metastatic compartments (MCs) at diagnosis either in bone marrow, in skeleton, or in another site with a range from 1 to 6 was calculated for each patient. The size of the treatment center was grouped up to 10 or > 10 according to the total number of patients treated at that center over the study period. The relationship between surgical excision and patient and treatment characteristics was evaluated using χ^2 test. Kendall's τ was used to explore the correlation between surgical excision and IDRFs and serious complications. Statistical analysis was performed with SAS 9.4 software (SAS Institute, Cary, NC), and the analysis was performed in August 2019.

RESULTS

The characteristics of the 1,531 patients who fulfilled the criteria (Data Supplement) are listed in Table 1. The median follow-up time after operation was 6.1 years. Patients were enrolled from 128 SIOPEN institutions (Data Supplement) in 18 countries using the SIOPEN-R-NET web-based system.³³

Time Point of Operation

Surgical resection was attempted at the EO in 923 patients (60%), after TVD in 393 (26%), and after HDT in 215 (14%; Table 1; Fig 1).

Outcome of Operation

CME was achieved in 1,172 patients (77%) and IME in 359 (23%). There was CME in 85% in the absence of IDRFs compared with 74% in their presence ($P < .001$). CME was higher in patients with adrenal compared with nonadrenal abdominal tumors ($P < .001$) and with *MYCN*-amplified tumors (Table 1). Treatment period, timing of operation, and treatment center size were not significantly related to the CME (Table 1).

Surgical Complications

There were 7 operation-related deaths (0.46%): intestinal ischemia ($n = 2$), major vascular injury ($n = 2$), liver ischemia ($n = 1$), bilateral renal ischemia ($n = 1$), and multisystem organ failure ($n = 1$). There was no difference in the number of operative deaths between CME (3 [0.26%] of 1,172 patients) and IME (4 [1.1%] of 359 patients; $P = .056$ by Fisher's exact test). Data on operative severe complications were available for 1,464 patients (96%). Severe surgical complications (not including nephrectomy) occurred in 142 (9.7%) of 1,464 patients, 89 (7.9%) of 1,128 with CME, and 53 (15.8%) of 336 with IME ($P < .001$). Nephrectomy was performed in 124 (8.8%) and was significantly less with CME (86 [7.9%] of 1,083) v 38 (11.9%) of 319 with IME ($P = .028$). Twenty of 142 patients with severe complications also had a nephrectomy. The relationship among extent of surgical resection, IDRFs, and severe complications is shown in the Data Supplement.

TABLE 1. Patient Characteristics and Treatment

Characteristic and Treatment	Total, No.	CME, No. (%)	IME, No. (%)	<i>P</i> ^a
No. of patients	1,531	1,172 (77)	359 (23)	
Sex				
Female	626	463 (74)	163 (26)	.0470
Male	905	709 (78)	196 (22)	
Age, years				
< 1	77	63 (82)	14 (18)	.0050
1-1.5	148	123 (83)	25 (17)	
1.5-5	1,018	780 (77)	238 (23)	
> 5	288	206 (72)	82 (28)	
≤ 1.5	225	186 (83)	39 (17)	.0190
> 1.5	1,306	986 (75)	320 (25)	
INSS stage				
4	1,521	1,162 (76)	359 (24)	.0790
4S MNA	10	10 (100)	0 (0)	
<i>MYCN</i>				
MNA yes	622	502 (81)	120 (19)	.0030
MNA no	810	600 (74)	210 (26)	
Missing ^b	99	70 (71)	29 (29)	
Primary tumor site				
Cervical				
Yes	50	36 (72)	14 (28)	.4400
No	1,481	1,136 (77)	345 (23)	
Thoracic				
Yes	181	128 (71)	53 (29)	.0490
No	1,350	1,044 (77)	306 (23)	
Adrenal				
Yes	1,109	894 (81)	215 (19)	< .0001
No	422	278 (66)	144 (34)	
Nonadrenal abdominal				
Yes	491	341 (69)	150 (31)	< .0001
No	1,040	831 (80)	209 (20)	
Pelvic				
Yes	82	55 (67)	27 (33)	.0370
No	1,449	1,117 (77)	332 (23)	
IDRFs				
Yes	1,097	814 (74)	283 (26)	< .0001
No	337	287 (85)	50 (15)	
Missing ^b	97	71 (73)	26 (27)	
No. of MCs				
1	182	137 (75)	45 (25)	.6490
> 1	1,203	924 (77)	279 (23)	
Missing ^b	146	111 (76)	35 (24)	

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TABLE 1. Patient Characteristics and Treatment (continued)

Characteristic and Treatment	Total, No.	CME, No. (%)	IME, No. (%)	<i>P</i> ^a
TVD				
Not given	1,040	814 (78)	226 (22)	.0210
Given	491	358 (73)	133 (27)	
Surgery				
EOI < 60 days after cycle 8	923	723 (78)	200 (22)	.1280
After TVD or > 60 days after cycle 8	393	290 (74)	103 (26)	
After HDT	215	159 (74)	56 (26)	
Severe operative complications				
Yes	142	89 (63)	53 (37)	< .0010
No	1,322	1,039 (79)	283 (21)	
Missing ^b	67	44 (66)	23 (34)	
Nephrectomy				
Yes	124	86 (69)	38 (31)	.0280
No	1,278	997 (78)	281 (22)	
Missing ^b	129	89 (69)	40 (31)	
HDT				
BuMel	1,053	816 (77)	237 (23)	.3590
CEM	255	200 (78)	55 (22)	
Other	2	2 (100)	0 (0)	
No HDT	80	56 (70)	24 (30)	
Type of HDT missing ^b	141	98 (70)	43 (30)	
Radiotherapy				
Done	1,153	893 (77)	260 (23)	
Not done	156	116 (74)	40 (26)	.4560
Missing ^b	222	163 (73)	59 (27)	
Dinutuximab beta				
Given	407	317 (78)	90 (22)	.4580
Not given	1,124	855 (76)	269 (24)	
Metastatic CR at EOI				
Yes	468	365 (78)	103 (22)	.3580
No	950	720 (76)	230 (24)	
Missing ^b	113	87 (77)	26 (23)	
Treatment period				
June 2002-June 2009	743	574 (77)	169 (23)	.5280
July 2009-December 2015	788	598 (76)	190 (24)	
Center size, patients				
≤ 10	465	369 (79)	96 (21)	.0870
> 10	1,066	803 (75)	263 (25)	

Abbreviations: BuMel, busulphan and melphalan; CEM, carboplatin, etoposide, and melphalan; CME, complete macroscopic excision; CR, complete response; EOI, end of induction; HDT, high-dose therapy; IDRF, image-defined risk factor; IME, incomplete macroscopic excision; INSS, International Neuroblastoma Staging System; MC, metastatic compartment; MNA, *MYCN* amplification; TVD, topotecan, vincristine, and doxorubicin.

^a*P* values by χ^2 test.

^bPatients with missing values are not included in the calculation of the *P* value.

TABLE 2. Relationship Between EFS, OS, and CILP and Risk Factors

Risk Factor	EFS				OS			CILP		
	Patients, No.	Events, No.	5-Year pEFS, ± SE	P	Events, No.	5-Year pOS, ± SE	P	Local Recurrences, No.	5-Year CILP, ± SE	P
Surgical excision										
CME	1,172	701	0.40 ± 0.01	< .001	614	0.45 ± 0.01	.004	194	0.17 ± 0.01	< .001
IME	359	243	0.33 ± 0.03		217	0.37 ± 0.03		109	0.30 ± 0.02	
Age, years										
< 1	77	31	0.58 ± 0.06	.002	29	0.60 ± 0.06	.020	5	0.07 ± 0.03	.029
1-1.5	148	78	0.48 ± 0.04		71	0.51 ± 0.04		23	0.16 ± 0.03	
1.5-5	1,018	630	0.38 ± 0.02		552	0.43 ± 0.02		211	0.21 ± 0.01	
> 5	288	205	0.28 ± 0.03		179	0.34 ± 0.03		64	0.22 ± 0.02	
≤ 1.5	225	109	0.51 ± 0.03	.002	100	0.54 ± 0.03	.017	28	0.13 ± 0.02	.008
>1.5	1,306	835	0.36 ± 0.01		731	0.41 ± 0.01		275	0.21 ± 0.01	
MYCN										
MNA no	810	514	0.36 ± 0.02	.724	449	0.41 ± 0.02	.750	163	0.20 ± 0.01	.960
MNA yes	622	367	0.41 ± 0.02		333	0.45 ± 0.02		124	0.20 ± 0.02	
IDRFs										
No	337	196	0.42 ± 0.03	.140	170	0.48 ± 0.03	.116	57	0.17 ± 0.02	.145
Yes	1,097	684	0.38 ± 0.02		604	0.42 ± 0.02		224	0.20 ± 0.01	
MCs										
1	182	86	0.54 ± 0.04	< .001	77	0.57 ± 0.04	< .001	42	0.22 ± 0.03	.342
> 1	1,203	782	0.35 ± 0.01		695	0.40 ± 0.01		238	0.20 ± 0.01	
Cervical										
No	1,481	910	0.38 ± 0.01	.530	801	0.43 ± 0.01	.604	292	0.20 ± 0.01	.697
Yes	50	34	0.30 ± 0.07		30	0.34 ± 0.08		11	0.24 ± 0.06	
Thoracic										
No	1,350	824	0.39 ± 0.01	.223	729	0.43 ± 0.01	.516	255	0.19 ± 0.01	.015
Yes	181	120	0.32 ± 0.04		102	0.40 ± 0.04		48	0.27 ± 0.03	
Adrenal										
No	422	280	0.34 ± 0.02	.028	244	0.39 ± 0.03	.071	109	0.26 ± 0.02	.015
Yes	1,109	664	0.40 ± 0.02		587	0.45 ± 0.02		194	0.18 ± 0.01	
Nonadrenal abdominal										
No	1,040	635	0.39 ± 0.02	.342	567	0.43 ± 0.02	.813	195	0.19 ± 0.01	.134
Yes	491	309	0.37 ± 0.02		264	0.43 ± 0.02		108	0.22 ± 0.02	
Pelvic										
No	1,449	894	0.38 ± 0.01	.857	791	0.43 ± 0.01	.447	287	0.20 ± 0.01	.870
Yes	82	50	0.42 ± 0.06		40	0.50 ± 0.06		16	0.18 ± 0.04	
EOI metastatic response										
CR	468	270	0.42 ± 0.02	.011	246	0.46 ± 0.02	.102	93	0.20 ± 0.02	.687
Less than CR	950	606	0.36 ± 0.02		525	0.42 ± 0.02		194	0.21 ± 0.01	
Surgery										
EOI < 60 days after cycle 8	923	560	0.40 ± 0.02	.149	501	0.44 ± 0.02	.659	180	0.19 ± 0.01	.227

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TABLE 2. Relationship Between EFS, OS, and CILP and Risk Factors (continued)

Risk Factor	Patients, No.	EFS			OS			CILP		
		Events, No.	5-Year pEFS, ± SE	P	Events, No.	5-Year pOS, ± SE	P	Local Recurrences, No.	5-Year CILP, ± SE	P
After TVD or > 60 days after cycle 8	393	255	0.34 ± 0.02		215	0.40 ± 0.03		72	0.19 ± 0.02	
After HDT	215	129	0.40 ± 0.03		115	0.45 ± 0.04		51	0.24 ± 0.03	
Severe operative complications										
No	1,322	820	0.38 ± 0.01	.656	718	0.43 ± 0.01	.200	262	0.20 ± 0.01	.202
Yes	142	87	0.38 ± 0.04		84	0.40 ± 0.04		34	0.24 ± 0.04	
Nephrectomy										
No	1,278	791	0.38 ± 0.01	.649	695	0.43 ± 0.01	.460	251	0.20 ± 0.01	.307
Yes	124	78	0.36 ± 0.04		71	0.40 ± 0.05		29	0.23 ± 0.04	
Center size										
≤ 10	465	276	0.40 ± 0.02	.331	242	0.44 ± 0.02	.334	76	0.16 ± 0.02	.036
> 10	1,066	668	0.38 ± 0.02		589	0.42 ± 0.02		227	0.21 ± 0.01	
Treatment period										
2002-June 2009	743	524	0.32 ± 0.02	< .001	484	0.35 ± 0.02	< .001	172	0.23 ± 0.02	.004
July 2009-2015	788	420	0.45 ± 0.02		347	0.52 ± 0.02		131	0.17 ± 0.01	

Abbreviations: CILP, cumulative incidence of local progression; CME, complete macroscopic excision; CR, complete response; EFS, event-free survival; EOI, end of induction; HDT, high-dose therapy; IDRf, image-defined risk factor; IME, incomplete macroscopic excision; MC, metastatic compartment; MNA, MYCN amplification; OS, overall survival; pEFS, probability of event-free survival; pOS, probability of overall survival; TVD, topotecan, vincristine, and doxorubicin.

Influence of Surgical Excision

Five-year EFS (0.40 ± 0.01) and 5-year OS (0.45 ± 0.02) were significantly higher with CME compared with IME (5-year EFS, 0.33 ± 0.03 ; 5-year OS, 0.37 ± 0.03 ; $P < .001$ and $P = .004$; Table 2; Fig 2). Local recurrence (CILP) was significantly lower after CME (0.17 ± 0.01) compared with IME (0.30 ± 0.02 ; $P \leq .001$). Neither severe operative complications nor nephrectomy had a significant adverse effect on EFS or OS (Table 2). The EFS and OS of 16 patients with follow-up who had surgical resection but incomplete details of surgery were not significantly different from the 1,531 evaluable patients.

Influence of Immunotherapy

Between June 2002 and June 2009, 5-year EFS was 0.33 ± 0.02 after CME compared with 0.27 ± 0.03 with IME (hazard ratio [HR], 1.3; 95% CI, 1.0 to 1.6; $P = .030$ adjusted for age, MCs, and EOI metastatic response; Fig 3). Five-year OS was 0.36 ± 0.02 after CME compared with 0.29 ± 0.03 with IME (HR, 1.3; 95% CI, 1.0 to 1.6; $P = .039$ adjusted for age, MCs, and EOI metastatic response; Fig 3), and 5-year CILP was 0.20 ± 0.02 for patients with CME compared with 0.33 ± 0.04 for those with IME (HR, 2.1; 95% CI, 1.5 to 2.9; $P < .001$).

After the introduction of immunotherapy (June 2009), 5-year EFS was 0.47 ± 0.01 after CME and 0.39 ± 0.04 after IME (adjusted HR, 1.3; 95% CI, 1.0 to 1.6; $P = .038$), and 5-year OS was 0.54 ± 0.02 after CME and 0.45 ± 0.02 after IME (adjusted HR, 1.3; 95% CI, 1.0 to 1.7; $P = .049$). CILP was 0.14 ± 0.02 (CME) compared with 0.27 ± 0.03 (IME; HR, 1.8; 95% CI, 1.2 to 2.7; $P = .002$; Fig 3).

Univariable and Multivariable Analyses

Univariable analysis. The extent of excision, MYCN amplification, primary tumor site, age at presentation, number of MCs at diagnosis, presence of IDRf, EOI metastatic response, time point of operation, surgical complications, nephrectomy, center size, and treatment period were examined for their influence on EFS (Table 2). CME, age < 1.5 years, adrenal primary tumor, single MC, EOI metastatic response, and treatment between July 2009 and December 2015 were all associated with a superior EFS.

Multivariable analysis (Cox regression). Independent factors associated with superior EFS were CME, age < 1.5 years, single MC, treatment between July 2009 and December 2015, and EOI metastatic response (Table 3). Independent factors associated with superior OS were

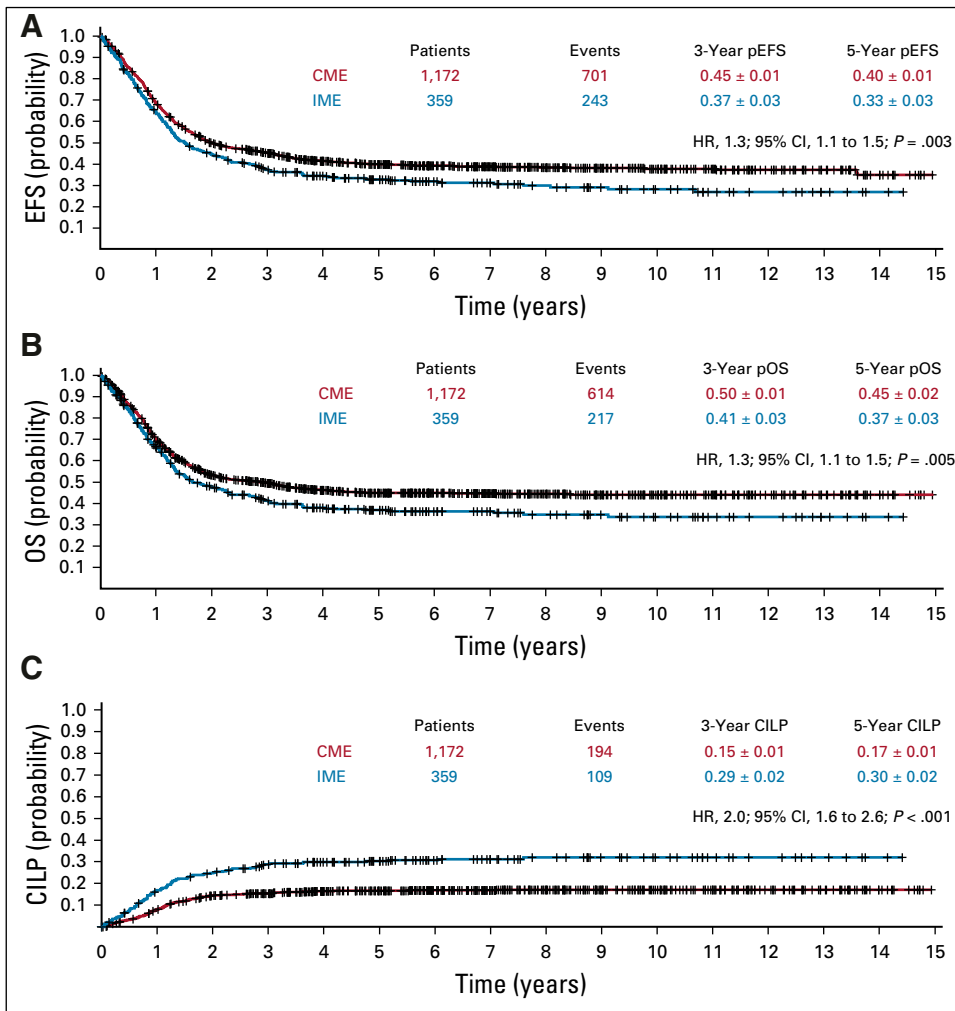


FIG 2. Outcome of the analysis population with complete macroscopic excision (CME) and incomplete macroscopic excision (IME). (A) Three- and 5-year event-free survival (EFS), (B) overall survival (OS), and (C) cumulative incidence of local progression (CILP). Hazard ratios (HRs) are adjusted for age, metastatic compartments, and end-of-induction metastatic response (complete response, yes/no; Table 3). pEFS, probability of event-free survival; pOS, probability of overall survival.

CME, single MC, and treatment period and for CILP, CME and treatment period.

DISCUSSION

This report demonstrates that patients in the HR-NBL1/SIOPEN trial with stage 4 high-risk neuroblastoma who had surgeon-assessed CME of the primary tumor had a significantly higher survival. This improvement in 5-year EFS and OS and lower local recurrence rate was evident in the pre-immunotherapy and immunotherapy eras and was achieved with a 9.7% severe operative complication rate and 0.46% operative mortality. The association of CME with improvement in EFS, OS, and CILP was further demonstrated by multivariable analysis (Table 3).

The efficacy of induction therapy in reducing primary tumor volume and vascularity, and thus allowing safer and effective excision, has been demonstrated in localized disease.³⁴ Although chemotherapy may reduce IDRFs, they are not usually eliminated.^{35,36} IDRFs were present in 77% of patients at surgery (Table 1) but were not considered

a contraindication to operation. IDRFs were identified by CT scanning, as supported by studies that have demonstrated that magnetic resonance imaging can underestimate IDRFs after induction chemotherapy.^{37,38} We found no relationship between IDRFs and survival; however, severe complications were more common in the presence of IDRFs (Data Supplement) and were less frequent with CME, which may reflect a better response to chemotherapy. The protocol advised against nephrectomy to preserve renal function for HDT/SCT, as supported by a study that found better survival in patients with bilateral renal preservation.³⁹ Nephrectomy was only undertaken to facilitate tumor excision, typically when the renal hilum was encased by tumor. It was performed in 8.8% of patients (Table 1) and was less frequent with CME compared with IME, possibly because these tumors were easier to resect. There was no difference in outcome (EFS, OS, and CILP) if excision was postponed until after HDT. Operation is feasible at this time but more challenging because the tumor is more solid and calcified. It is an option if operation before HDT is not believed achievable because of potential surgical

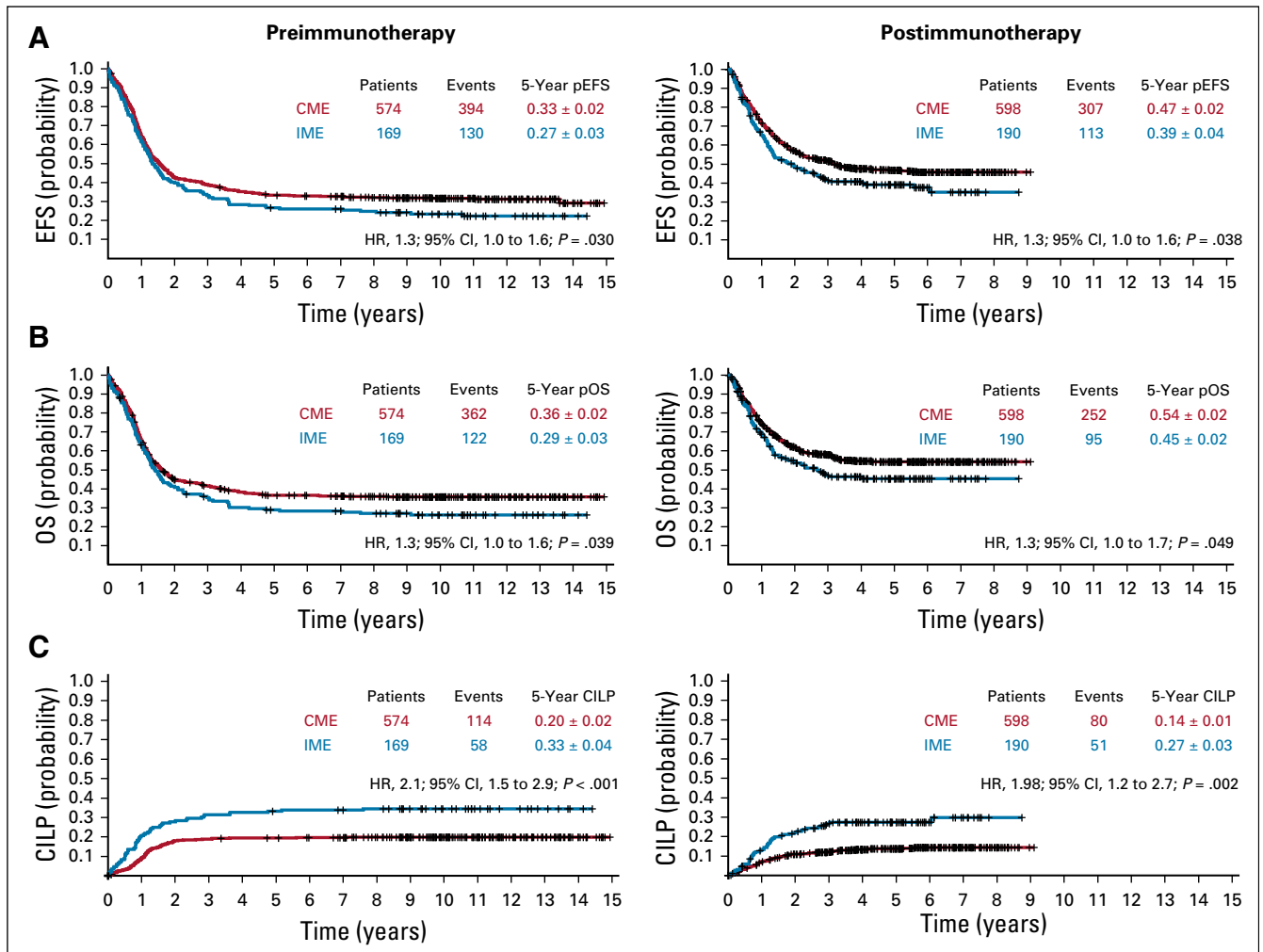


FIG 3. Outcome of the analysis population comparing pre-immunotherapy (June 2002-June 2009) and immunotherapy (July 2009-December 2015) periods. (A) Five-year event-free survival (EFS), (B) overall survival (OS), and (C) cumulative incidence of local progression (CILP). Hazard ratios (HRs) are adjusted for age, metastatic compartments, and end-of-induction metastatic response (complete response, yes/no; Table 3). CME, complete macroscopic excision; HR, hazard ratio; IME, incomplete macroscopic excision; pEFS, probability of event-free survival; pOS, probability of overall survival.

complications or nephrectomy. Our recommendation is that surgery be carried out as soon as technically feasible. Excision during induction was not considered because maintenance of the 10-day schedule of chemotherapy is crucial to achieve dose intensity. In addition, the data support operation at smaller centers by experienced surgeons, provided that they are SIOPEN-designated pediatric oncology centers.

The percentage of patients in whom CME was achieved (77%) is similar to that reported in a Children's Oncology Group study (70%).¹⁶ A higher frequency of CME with *MYCN*-amplified tumors may have been due to their having a greater mean reduction in primary tumor volume⁴⁰ and losing more IDR³⁵ compared with non-*MYCN*-amplified tumors after induction therapy.

In this study, the protocol advised irradiation at a dose of 21 Gy to the preoperative volume of the primary tumor

and involved lymph nodes after HDT/SCR, irrespective of the result of resection, although delivery of the full dose was not always possible because of the tolerance of organs at risk.⁴¹ Prophylactic radiotherapy was not given to uninvolved lymph nodes, a practice that has been supported by a retrospective analysis.⁴² Radiotherapy was withheld only if the radiotherapy coordinators considered that the site and volume of the primary tumor made radiotherapy a risk. This strategy differs from other studies¹⁴ where patients were irradiated, with a higher dose (40 Gy), if there was macroscopic postoperative residual disease. The evidence for the value of radiotherapy in high-risk neuroblastoma is limited,⁴³ and a prospective randomized trial is required to define precisely the benefit. Defining the individual roles of the completeness of surgical resection and radiotherapy in local control is challenging because the effects of the two modalities are intricately intermixed.

TABLE 3. Multivariate Analysis of Risk Factors in Stage 4 High-Risk Neuroblastoma

Model	EFS		OS		CILP	
	P	HR (95% CI)	P	HR (95% CI)	P	Subdistribution HR (95% CI)
A. Total (n = 1,297)						
Age at diagnosis, years						
≤ 1.5		1		1		1
> 1.5	.0370	1.3 (1 to 1.6)	.1450	1.2 (0.9 to 1.5)	.0800	1.4 (1 to 2.2)
MCs						
1		1		1		1
> 1	< .0001	1.8 (1.4 to 2.2)	< .0001	1.8 (1.4 to 2.3)	.5920	0.9 (0.7 to 1.3)
Treatment period						
≥ July 2009		1		1		1
< June 2009	< .0001	1.5 (1.3 to 1.7)	< .0001	1.6 (1.4 to 1.9)	.0070	1.4 (1.1 to 1.8)
EOI metastatic response						
CR		1		1		1
< CR	.0430	1.2 (1 to 1.4)	.2000	1.1 (0.9 to 1.3)	.9340	1 (0.8 to 1.3)
Surgical result						
CME		1		1		1
IME	.0030	1.3 (1.1 to 1.5)	.0050	1.3 (1.1 to 1.5)	< .0001	2 (1.5 to 2.5)
B. 2002-June 2009 (n = 656)						
Age at diagnosis, years						
≤ 1.5		1		1		1
> 1.5	.0260	1.4 (1 to 2)	.0300	1.4 (1 to 2)	.5500	1.2 (0.7 to 2)
MCs						
1		1		1		1
> 1	< .0001	1.7 (1.3 to 2.3)	< .0001	1.8 (1.3 to 2.4)	.2510	0.8 (0.5 to 1.2)
EOI metastatic response						
CR		1		1		1
< CR	.0690	1.2 (1 to 1.5)	.2580	1.1 (0.9 to 1.4)	.6400	0.9 (0.7 to 1.3)
Surgical result						
CME		1		1		1
IME	.0300	1.3 (1 to 1.6)	.0390	1.3 (1 to 1.6)	< .0001	2.1 (1.5 to 2.9)
C. July 2009-2015 (n = 641)						
Age at diagnosis, years						
≤ 1.5		1		1		1
> 1.5	.5010	1.1 (0.8 to 1.5)	.8340	1 (0.7 to 1.3)	.0770	1.8 (0.9 to 3.4)
MCs						
1		1		1		1
> 1	.0080	1.9 (1.2 to 2.9)	.0140	1.9 (1.1 to 3.1)	.3600	1.4 (0.7 to 3.1)
EOI metastatic response						
CR		1		1		1
< CR	.3050	1.1 (0.9 to 1.4)	.4750	1.1 (0.9 to 1.4)	.4140	1.2 (0.8 to 1.8)
Surgical result						
CME		1		1		1
IME	.0380	1.3 (1 to 1.6)	.0490	1.3 (1 to 1.7)	.0020	1.8 (1.2 to 2.7)

NOTE. Risk factors that were not significant (at the 5 level) for EFS in the univariable analysis (Table 2; *MYCN* amplification, primary tumor site, presence of IDRFs, time point of operation, surgical complications, nephrectomy, center size) were not included in the multivariable analysis.

Abbreviations: CILP, cumulative incidence of local progression; CME, complete macroscopic excision; CR, complete response; EFS, event-free survival; EOI, end of induction; HR, hazard ratio; IDRF, image-defined risk factor; IME, incomplete macroscopic excision; MC, metastatic compartment; OS, overall survival.

The added benefit of surgical excision to survival in high-risk neuroblastoma is difficult to delineate, and there are conflicting reports.⁹⁻¹⁹ Consistent with a systematic review¹⁹ and many reports,^{9-12,15,16} we were able to demonstrate a significantly lower incidence of local disease progression (CILP) after CME compared with IME (Fig 2). In contrast to this analysis, a report from the German Society for Pediatric Oncology and Hematology (GPOH)¹⁴ in which only 28 (10%) of 278 patients received radiotherapy demonstrated that 54.7% of patients had complete excision after induction chemotherapy but showed no relationship between the extent of surgical excision and survival. Our results are corroborated by the previous findings of the COG A3973 trial¹⁶ and are complementary, rather than contradictory, to the results of the GPOH NB97 study, which suggests that the combination of surgery with radiotherapy is required to achieve local control in high-risk neuroblastoma.^{16,44,45} Supportive data for an improved local control rate after radiotherapy were also demonstrated in the CCG-3891 trial.¹⁶ This might argue for a higher dose of radiotherapy in patients with macroscopic residual disease and will be a randomized question in the next SIOPEN high-risk neuroblastoma trial.

It is possible that CME is associated with favorable tumor biologic features and that tumor biology is driving both the ease of achieving a CME and better survival. However, this cannot be assessed in the current analysis, and to date, these favorable tumor biologic features and relationship with age have not been identified.

Assessment of CME and IME was based on surgeon assessment at the conclusion of operation, and the volume of the residue was not quantified. When designing the trial, the trial radiology committee did not consider that contemporary imaging would discriminate between residual

disease and the tissue effects of operation. This is supported by studies (including a contemporary European study; S. Irtan, personal communication, April 2020) where discordance was found in 33%, 37%, and 42% of patients when the degree of resection was determined by postoperative imaging and surgical assessment.^{16,46} The discordance may be due to variation in the time of imaging and different imaging techniques, and that any imaging technique, except positive tumor avidity on MIBG single-photon emission CT may not be sufficiently accurate to discriminate tumor from the effects of operation. In the next SIOPEN high-risk study, HR-NBL2, postoperative cross-sectional imaging at a specified time is planned to compare surgically assessed resection with that determined by imaging. Histopathologic examination of the resected specimen cannot confirm the completeness of excision because tumors are usually not removed *en bloc*, and the clear margins used to define complete excision in other tumor types cannot be applied to neuroblastoma, where the tumor margin is often the wall of a major blood vessel. The proposed consensus on surgical terminology will facilitate comparisons between reports of investigations by international trial cooperative groups.⁴⁷

To our knowledge, this study of 1,531 patients is the largest analysis of the influence of surgical excision on the survival of patients with stage 4 high-risk neuroblastoma in a single trial to date. An improvement in survival and a reduction in local progression were associated with CME and radiotherapy to the preoperative volume of the primary tumor and involved regional lymph nodes. Furthermore, the association of CME with a superior outcome persisted with immunotherapy using dinutuximab beta. In conclusion, the low severe operative complication and mortality rates justify determined attempts at CME of the primary tumor after appropriate chemotherapy.

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PRIOR PRESENTATION

Presented at the American Society of Clinical Oncology 2017 Annual Meeting, Chicago, IL, June 2-6, 2017, and International Society of Paediatric Oncology 2018, Kyoto, Japan, November 16-19, 2018.

SUPPORT

Supported in part by European Commission 5th Framework Grant No. QLRI-CT-2002-01768 (SIOPEN-R NET www.siopen-r-net.org), and Pierre Fabre Médicament provided free drug supply of Busilvex. M.N.G. is supported by the National Institute for Health Research University College London Hospitals Biomedical Research Centre.

CLINICAL TRIAL INFORMATION

[NCT01704716](https://clinicaltrials.gov/ct2/show/study/NCT01704716) and EudraCT 2006-001489-17.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI <https://doi.org/10.1200/JCO.19.03117>.

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REFERENCES

- Ladenstein R, Pötschger U, Pearson ADJ, et al: Busulfan and melphalan versus carboplatin, etoposide, and melphalan as high-dose chemotherapy for high-risk neuroblastoma (HR-NBL1/SIOPEN): An international, randomised, multi-arm, open-label, phase 3 trial. *Lancet Oncol* 18:500-514, 2017
- Ladenstein RL, Pötschger U, Valteau-Couanet D, et al: Multi-centre, randomised, phase 3 trial of Interleukin-2 with anti-G2 Antibody ch14.18/CHO (dinutuximab beta) in high-risk neuroblastoma patients. Results from the HR-NBL1/SIOPEN trial. *Lancet Oncol* 19:1617-1629, 2018
- Matthay KK, Reynolds CP, Seeger RC, et al: Long-term results for children with high-risk neuroblastoma treated on a randomized trial of myeloablative therapy followed by 13-cis-retinoic acid: A Children's Oncology Group study. *J Clin Oncol* 27:1007-1013, 2009
- Yu AL, Gilman AL, Ozkaynak MF, et al: Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. *N Engl J Med* 363:1324-1334, 2010
- Kreissman SG, Seeger RC, Matthay KK, et al: Purged versus non-purged peripheral blood stem-cell transplantation for high-risk neuroblastoma (COG A3973): A randomised phase 3 trial. *Lancet Oncol* 14:999-1008, 2013
- Park JR, Kreissman SG, London WB, et al: Effect of tandem autologous stem cell transplant vs single transplant on event-free survival in patients with high-risk neuroblastoma: A randomized clinical trial. *JAMA* 322:746-755, 2019
- Pearson AD, Pinkerton CR, Lewis IJ, et al: High-dose rapid and standard induction chemotherapy for patients aged over 1 year with stage 4 neuroblastoma: A randomised trial. *Lancet Oncol* 9:247-256, 2008
- Haase GM, O'Leary, Ramsay NK, et al: Aggressive surgery combined with intensive chemotherapy improves survival in poor risk neuroblastoma. *J Pediatr Surg* 26:1119-1123, 1991
- Adkins ES, Sawin R, Gerbing RB, et al: Efficacy of complete resection for high-risk neuroblastoma: A Children's Cancer Group study. *J Pediatr Surg* 39:931-936, 2004
- La Quaglia MP, Kushner BH, Su W, et al: The impact of gross total resection on local control and survival in high-risk neuroblastoma. *J Pediatr Surg* 39:412-417, 2004; discussion 412-417
- McGregor LM, Rao BN, Davidoff AM, et al: The impact of early resection of primary neuroblastoma on the survival of children older than 1 year of age with stage 4 disease: The St. Jude Children's Research Hospital experience. *Cancer* 104:2837-2846, 2005
- Sultan I, Ghandour K, Al-Jumaily U, et al: Local control of the primary tumour in metastatic neuroblastoma. *Eur J Cancer* 45:1728-1732, 2009
- Rich BS, McEvoy MP, Kelly NE, et al: Resectability and operative morbidity after chemotherapy in neuroblastoma patients with encasement of major visceral arteries. *J Pediatr Surg* 46:103-107, 2011
- Simon T, Häberle B, Hero B, et al: Role of surgery in the treatment of patients with stage 4 neuroblastoma age 18 months or older at diagnosis. *J Clin Oncol* 31:752-758, 2013
- Cai J, Pan C, Tang Y, et al: Multivariate analysis of risk factors for patients with stage 4 neuroblastoma who were older than 18 months at diagnosis: A report from a single institute in Shanghai, China. *J Cancer Res Clin Oncol* 143:1327-1335, 2017

16. von Allmen D, Davidoff AM, London WB, et al: Impact of extent of resection on local control and survival in patients from the COG A3973 study with high-risk neuroblastoma. *J Clin Oncol* 35:208-216, 2017
17. Kaneko M, Ohakawa H, Iwakawa M: Is extensive surgery required for treatment of advanced neuroblastoma? *J Pediatr Surg* 32:1616-1619, 1997
18. Browne M, Kletzel M, Cohn SL, et al: Excellent local tumor control regardless of extent of surgical resection after treatment on the Chicago Pilot II protocol for neuroblastoma. *J Pediatr Surg* 41:271-276, 2006
19. Yang X, Chen J, Wang N, et al: Impact of extent of resection on survival in high-risk neuroblastoma: A systematic review and meta-analysis. *J Pediatr Surg* 54:1487-1494, 2019
20. Ladenstein R, Valteau-Couanet D, Brock P, et al: Randomized trial of prophylactic granulocyte colony-stimulating factor during rapid COJEC induction in pediatric patients with high-risk neuroblastoma: The European HR-NBL1/SIOPEN study. *J Clin Oncol* 28:3516-3524, 2010
21. Amoroso L, Erminio G, Makin G, et al: Topotecan-vincristine-doxorubicin in stage 4 high risk neuroblastoma patients failing to achieve a complete metastatic response to rapid COJEC - A SIOPEN Study. *Cancer Res Treat* 50:148-155, 2018
22. Ambros IM, Benard J, Boavida M, et al: Quality assessment of genetic markers used for therapy stratification. *J Clin Oncol* 21:2077-2084, 2003
23. Ambros PF, Ambros IM, Brodeur GM, et al: International consensus for neuroblastoma molecular diagnostics: Report from the International Neuroblastoma Risk Group (INRG) Biology Committee. *Br J Cancer* 100:1471-1482, 2009
24. Brodeur GM, Pritchard J, Berthold F, et al: Revisions of the international criteria for neuroblastoma diagnosis, staging, and response to treatment. *J Clin Oncol* 11:1466-1477, 1993
25. Cecchetto G, Mosseri V, De Bernardi B, et al: Surgical risk factors in primary surgery for localized neuroblastoma: The LNESG1 study of the European International Society of Pediatric Oncology Neuroblastoma Group. *J Clin Oncol* 23:8483-8489, 2005
26. Monclair T, Brodeur GM, Ambros PF, et al: The International Neuroblastoma Risk Group (INRG) staging system: An INRG task force report. *J Clin Oncol* 27:298-303, 2009
27. Brisse HJ, McCarville MB, Granata C, et al: Guidelines for imaging and staging of neuroblastic tumors: Consensus report from the International Neuroblastoma Risk Group Project. *Radiology* 261:243-257, 2011
28. Cohn SL, Pearson AD, London WB, et al: The International Neuroblastoma Risk Group (INRG) classification system: An INRG task force report. *J Clin Oncol* 27:289-297, 2009
29. Kiely E: A technique for excision of abdominal and pelvic neuroblastomas. *Ann R Coll Surg Engl* 89:342-348, 2007
30. Schemper M, Smith TL: A note on quantifying follow-up in studies of failure time. *Control Clin Trials* 17:343-346, 1996
31. Marubini EV: *Analysing Survival Data from Clinical Trials and Observational Studies*. New York, NY, Wiley, 2004
32. Gray RJ: A class of k-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat* 16:1611-161154, 1988
33. SIOPEN-R-Net: International Society of Paediatric Oncology European Neuroblastoma Research Network. <https://www.siopen-r-net.org>
34. von Schweinitz D, Hero B, Berthold F: The impact of surgical radicality on outcome in childhood neuroblastoma. *Eur J Pediatr Surg* 12:402-409, 2002
35. Irtan S, Brisse HJ, Minard-Colin V, et al: Image-defined risk factor assessment of neurogenic tumors after neoadjuvant chemotherapy is useful for predicting intra-operative risk factors and the completeness of resection. *Pediatr Blood Cancer* 62:1543-1549, 2015
36. Avanzini S, Pio L, Erminio G, et al: Image-defined risk factors in unresectable neuroblastoma: SIOPEN study on incidence, chemotherapy-induced variation, and impact on surgical outcomes. *Pediatr Blood Cancer* 64:e26605, 2017
37. Burnand K, Barone G, McHugh K, et al: Preoperative computed tomography scanning for abdominal neuroblastomas is superior to magnetic resonance imaging for safe surgical planning. *Pediatr Blood Cancer* 66:e27955, 2019
38. Bagatell R, McHugh K, Naranjo A, et al: Assessment of primary site response in children with high-risk neuroblastoma: An international multicenter study. *J Clin Oncol* 34:740-746, 2016
39. Tsuchida Y, Yokoyama J, Kaneko M, et al: Therapeutic significance of surgery in advanced neuroblastoma: A report from the study group of Japan. *J Pediatr Surg* 27:616-622, 1992
40. Yanishevski D, McCarville MB, Doubrovin M, et al: Impact of MYCN status on response of high-risk neuroblastoma to neoadjuvant chemotherapy. *J Pediatr Surg* 55:130-134, 2020
41. Gaze MN, Boterberg T, Dieckmann K, et al: Results of a quality assurance review of external beam radiation therapy in the International Society of Paediatric Oncology (Europe) Neuroblastoma Group's High-Risk Neuroblastoma Trial: A SIOPEN study. *Int J Radiat Oncol Biol Phys* 85:170-174, 2013
42. Braunstein SE, London WB, Kreissman SG, et al: Role of the extent of prophylactic regional lymph node radiotherapy on survival in high-risk neuroblastoma: A report from the COG A3973 study. *Pediatr Blood Cancer* 66:e27736, 2019
43. Arumugam S, Manning-Cork NJ, Gains JE, et al: The evidence for external beam radiotherapy in high-risk neuroblastoma of childhood: A systematic review. *Clin Oncol (R Coll Radiol)* 31:182-190, 2019
44. Stenman J, Herold N, Svensson PJ, et al: Improved local control by extensive surgery in high-risk neuroblastoma may be dependent on adjuvant radiotherapy. *J Clin Oncol* 35:1965-1966, 2017
45. Haas-Kogan DA, Swift PS, Selch M, et al: Impact of radiotherapy for high-risk neuroblastoma: A Children's Cancer Group study. *Int J Radiat Oncol Biol Phys* 56:28-39, 2003
46. von Allmen D, Grupp S, Diller L, et al: Aggressive surgical therapy and radiotherapy for patients with high-risk neuroblastoma treated with rapid sequence tandem transplant. *J Pediatr Surg* 40:936-941, discussion 941, 2005
47. Matthysens LE, Nuchtern JG, Van de Ven CP, et al: The International Neuroblastoma Surgical Report Form (INSRF): Novel standard for systematic reporting of neuroblastoma surgery: A joint initiative by the paediatric oncological cooperative groups SIOPEN, COG and GPOH. *Ann Surg* (in press).



AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Influence of Surgical Excision on the Survival of Patients With Stage 4 High-Risk Neuroblastoma: A Report From the HR-NBL1/SIOPEN Study**

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Uncompensated Relationships: Advanced Accelerator Applications

Martin Elliott

Consulting or Advisory Role: Bayer AG

Shifra Ash

Travel, Accommodations, Expenses: Bayer AG

Walentyna Balwierz

Honoraria: Shire, Gilead Sciences
Consulting or Advisory Role: Amgen, Novartis, Roche
Travel, Accommodations, Expenses: Jazz Pharmaceuticals, Shire, Roche, SERVIER

Vassilios Papadakis

Honoraria: EUSA Pharma, Novartis, Novartis (I)
Consulting or Advisory Role: SOBI
Travel, Accommodations, Expenses: Sanofi, Gilead Sciences, Novartis, Astellas Pharma

Toby Trahair

Stock and Other Ownership Interests: CSL Limited, Osteopore, Medical Developments International
Consulting or Advisory Role: Ipsos

Mark N. Gaze

Research Funding: Bristol-Myers Squibb (Inst), EUSA Pharma (Inst)
Travel, Accommodations, Expenses: Adienne Pharma & Biotech

Dominique Valteau-Couanet

Consulting or Advisory Role: EUSA Pharma (Inst)
Research Funding: Orphelia (Inst)
Patents, Royalties, Other Intellectual Property: Royalties from APEIRON Biologics to SIOPEN (Inst)
Travel, Accommodations, Expenses: EUSA Pharma, Jazz Pharmaceuticals

Ruth Lydia Ladenstein

Honoraria: APEIRON Biologics, Boehringer Ingelheim, EUSA Pharma
Consulting or Advisory Role: APEIRON Biologics, Boehringer Ingelheim, EUSA Pharma (Inst)
Research Funding: APEIRON Biologics (Inst), EUSA Pharma (Inst)
Patents, Royalties, Other Intellectual Property: APEIRON Biologics (Inst), EUSA Pharma (Inst)
Expert Testimony: APEIRON Biologics, EUSA Pharma
Travel, Accommodations, Expenses: APEIRON Biologics, EUSA Pharma

No other potential conflicts of interest were reported.