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Prospective Evaluation of Radiation Dose Escalation in Patients With High-Risk Neuroblastoma and Gross Residual Disease After Surgery: A Report From the Children's Oncology Group ANBL0532 Study

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abstract

PURPOSE A primary objective of the Children's Oncology Group (COG) ANBL0532 phase III study was to assess the effect of increasing local dose of radiation to a residual primary tumor on the cumulative incidence of local progression (CILP) in patients with high-risk neuroblastoma.

PATIENTS AND METHODS Newly diagnosed patients with high-risk neuroblastoma were randomly assigned or assigned to receive single or tandem autologous stem-cell transplantation (SCT) after induction chemotherapy. Local control consisted of surgical resection during induction chemotherapy and radiotherapy after last SCT. Patients received 21.6 Gy to the preoperative primary tumor volume. For patients with incomplete surgical resection, an additional boost of 14.4 Gy was delivered to the gross residual tumor, for a total dose of 36 Gy. CILP (primary end point) and event-free (EFS) and overall survival (OS; secondary end points) were compared with the COG A3973 historical cohort, in which all patients received single SCT and 21.6 Gy without a boost.

RESULTS For all patients in ANBL0532 receiving radiotherapy (n = 323), 5-year CILP, EFS, and OS rates were 11.2% ± 1.8%, 56.2% ± 3.4%, and 68.4% ± 3.2% compared with 7.1% ± 1.4% (P = .0590), 47.0% ± 3.5% (P = .0090), and 57.4% ± 3.5% (P = .0088) for all patients in A3973 receiving radiotherapy (n = 328), respectively. Five-year CILP, EFS, and OS rates for patients in A3973 with incomplete resection and radiotherapy (n = 47) were 10.6% ± 4.6%, 48.9% ± 10.1%, and 56.9% ± 10.0%, respectively. In comparison, 5-year CILP, EFS, and OS rates for patients in ANBL0532 who were randomly assigned or assigned to single SCT and received boost radiotherapy (n = 74) were 16.3% ± 4.3% (P = .4126), 50.9% ± 7.0% (P = .5084), and 68.1% ± 6.7% (P = .2835), respectively.

CONCLUSION Boost radiotherapy to gross residual tumor present at the end of induction did not significantly improve 5-year CILP. These results highlight the need for new strategies to decrease the risk of locoregional failure.

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ASSOCIATED CONTENT

Appendix

Protocol

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

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INTRODUCTION

Neuroblastoma is a tumor that originates from the developing sympathetic nervous system and is the most common extracranial solid malignancy occurring in childhood.[1] For patients with high-risk neuroblastoma, a multimodal approach is used, including intensive chemotherapy, multiagent myeloablative regimens, surgery, radiotherapy, and immunotherapy. Outcomes for this group remain inadequate, with overall survival (OS) of approximately 50% at 5 years.[2-5] Locoregional relapse continues to be a significant contributor to treatment failure, even after radiotherapy.[6-9]

Current approaches to local therapy for patients with incomplete resection remain inadequate, with 5-year cumulative incidence of local progression (CILP) of approximately 20% for patients with an extent of resection < 90%.[4,6,10] Prior studies suggest that radiation dose escalation can improve outcomes for patients with high-risk neuroblastoma.[2,11-14] In particular, Simon et al[15] demonstrated delivery of 30.6 to 40 Gy to the residual tumor volume resulted in event-free survival (EFS) and OS rates similar to those in patients without residual disease after induction chemotherapy with limited acute or late toxicity,

CONTEXT

Key Objective

Does increasing local dose of radiation to a residual primary tumor improve the cumulative incidence of local progression (CILP) in patients with high-risk neuroblastoma after surgery?

Knowledge Generated

We studied this question prospectively in the Children's Oncology Group (COG) ANBL0532 phase III study using a historical comparison cohort, COG A3973, that underwent single stem-cell transplantation (SCT) and did not receive boost radiotherapy. Five-year CILP, event-free survival, and overall survival were not statistically different between patients who received single SCT and boost radiotherapy in ANBL0532 and those with incomplete resection and no boost radiotherapy in A3973.

Relevance

Boost radiotherapy for gross residual disease does not improve local control, and this strategy is not recommended. New strategies are needed to decrease the risk of locoregional failure.

suggesting dose escalation may effectively and safely treat gross residual tumor. However, these prior reports are limited by retrospective study designs and small sample sizes; therefore, a large prospective cooperative group study is needed to answer this critically important question.

Given the high rates of local recurrence after incomplete surgical resection and the anticipated acceptable toxicity associated with a modest radiation dose escalation, Children's Oncology Group (COG) ANBL0532 prospectively evaluated the potential benefit of boost radiotherapy for patients with gross residual tumor. All patients received 21.6 Gy of radiation to the preoperative primary tumor volume after induction chemotherapy. For patients with incomplete resection, an additional boost of 14.4 Gy (for total dose of 36 Gy) was delivered only to gross residual tumor volume. Similar to the preceding COG clinical trial for high-risk neuroblastoma, COG A3973, evaluation of incomplete resection was performed after 5 cycles of induction chemotherapy and before stem-cell transplantation (SCT). In this report, we describe results of a preplanned comparison with COG A3973 to evaluate the potential benefit of radiation dose escalation to improve outcomes of patients with high-risk neuroblastoma and incomplete resection of their primary tumor.[4,5,16]

PATIENTS AND METHODS

Patients and Treatment

Newly diagnosed patients with high-risk neuroblastoma were enrolled in ANBL0532 from November 2007 to February 2012.[17] Patients or parents/guardians provided written informed consent in accordance with the institutional review board at each site.

Of the 652 eligible patients enrolled in ANBL0532, 382 were assigned to single SCT (n = 27) or randomly assigned to single or tandem SCT (n = 355).[17] Patients who received radiotherapy on study were eligible for analysis. Local control consisted of surgical resection planned after 5 cycles of induction chemotherapy and radiotherapy after recovery from last planned autologous SCT. Induction chemotherapy regimens were similar to that of COG A3973, with the exception of the first 2 cycles, which consisted of topotecan plus cyclophosphamide in ANBL0532 and cyclophosphamide, doxorubicin, and vincristine in A3973.[4,5,17] Surgical guidelines were identical to those used in COG A3973.[4,5] Patients were prescribed 21.6 Gy in 1.8 Gy daily fractions to the preoperative primary tumor volume after induction chemotherapy. For patients with an incomplete resection of the primary tumor (defined as > 1 cm^3 residual soft tissue density on end-induction scans), a boost of 14.4 Gy in 1.8 Gy daily fractions, for a total dose of 36 Gy, was delivered to gross residual tumor volume (Fig 1). Patients received radiotherapy no sooner than 28 days after transplantation. Of note, 29 patients with incomplete resection did not receive radiotherapy on study. Patients with metaiodobenzylguanidine (MIBG) -avid metastatic sites documented during postinduction and pretransplantation imaging were to receive irradiation of metastatic sites. Central review of all radiotherapy plans was performed. Plans with major or minor deviations as defined in the protocol were noted (Data Supplement). For patients with complete response or gross total resection of primary tumor reported postinduction with a negative MIBG scan, central radiology review was performed.

The historical control group consisted of 328 patients who were enrolled in COG A3973 and received radiotherapy (Fig 1).[16] A3973 randomly assigned patients to single SCT with or without tumor-selective purging of autologous hematopoietic stem-cell product and found no difference between the 2 groups[5]; therefore, we included all patients with purged or unpurged transplantation. Central review of all radiotherapy plans was performed for A3973. Patients received 21.6 Gy in 1.8 Gy daily fractions to the preoperative primary tumor volume after induction chemotherapy and

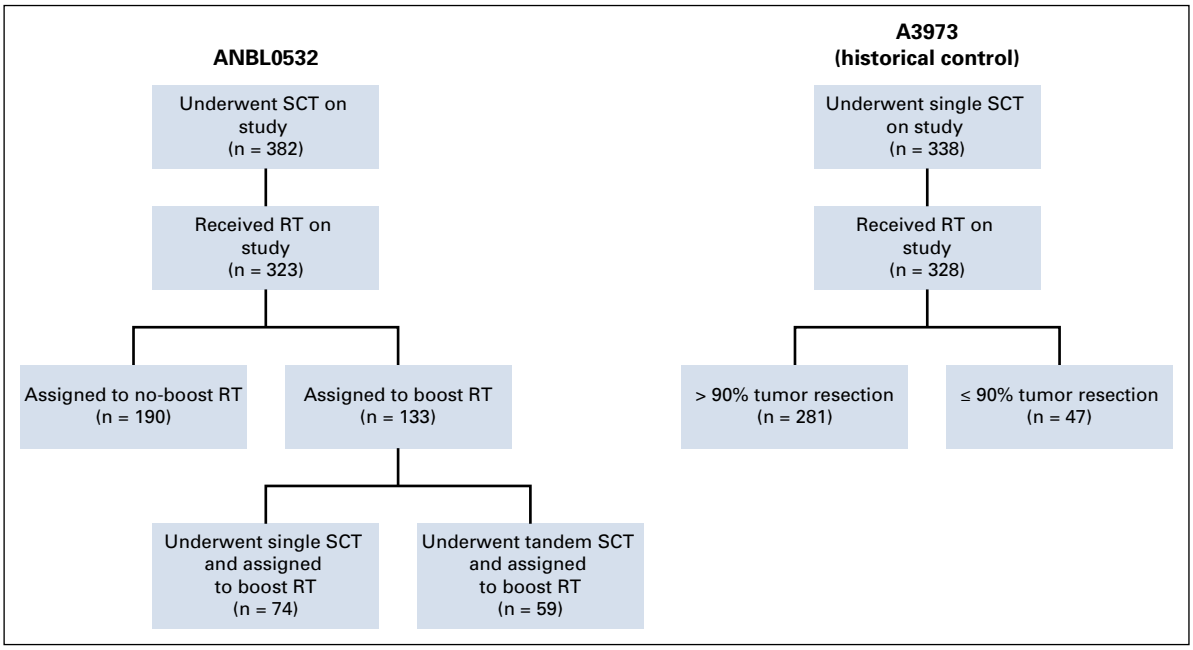


FIG 1. CONSORT diagram depicting the Children's Oncology Group (COG) ANBL0532 and COG A3973 patient cohorts for analysis. RT, radiotherapy; SCT, stem-cell transplantation.

MIBG-positive metastatic sites documented during the postinduction and pretransplantation imaging. All patients were to undergo radiotherapy after recovery from single SCT. Of the patients who received radiotherapy in A3973, 47 had residual disease, as defined by ≤ 90% primary tumor resection assessed by the surgeon at time of surgery, with 46 of these patients confirmed by central surgical review.[4,16] This subgroup of patients in A3973 would have received an additional boost had they been enrolled in ANBL0532 and therefore formed an additional comparator subgroup.

After radiotherapy, all patients in ANBL0532 and A3973 received isotretinoin alone or were enrolled in the COG ANBL0032 or ANBL0931 trial, which included interleukin-2, granulocyte-macrophage colony-stimulating factor, and dinutuximab, an antidisialoganglioside (GD2) chimeric antibody, in addition to isotretinoin.[18,19]

Statistical Analyses

The primary end point was CILP, defined as time from start of radiotherapy until first occurrence of relapse or disease progression at the primary site and/or locoregional lymph nodes, including events that occurred concurrently with distant relapse or progression. Isolated distant failure, secondary malignancy, and death as first event were considered competing risks. Secondary end points were EFS and OS, defined as time from start of radiotherapy to first occurrence of relapse, progression, secondary malignancy, or death, and death, respectively. For post hoc analysis, cumulative incidence of metastatic progression (CIMP) was defined as time from start of radiotherapy until first occurrence of metastatic relapse or disease progression, including events that occurred concurrently with local relapse or progression. Isolated local relapse or progression, secondary malignancy, and death as first event were considered competing risks. For CILP, CIMP, EFS, and OS, patients without an event were censored at last follow-up. CILP and CIMP were compared using Gray's test. Kaplan-Meier curves and log-rank tests were used to determine and compare EFS and OS, with standard errors calculated per Peto et al.[20,21] Patient baseline characteristics were compared between groups using Fisher's exact or χ^2 test as appropriate depending on sample size.

For post hoc analysis, lymph node coverage (LNC) was estimated in 4 anatomic regions (para-aortic, pelvic, mediastinal, and cervical), and per-patient average percentage LNC was calculated using 2 different approaches. Method A weighed all regions equally, and method B assessed only the lymph node region that conformed to the primary tumor location. CILP, EFS, and OS for patients in ANBL0532 were compared by percentage of LNC with cutoffs of 10%, 15%, and 20% using both methods.[16]

All statistical analyses were performed by intention to treat in those patients who received radiotherapy using SAS software (version 9.4), and R software (https://www.r-project.org/) was used to generate survival curves. P values $< .05$ were considered statistically significant.

RESULTS

Patient Characteristics

Analytic cohorts were composed of 323 and 328 patients who received radiotherapy in ANBL0532 and A3973, respectively (Fig 1). Baseline characteristics between patients

receiving radiotherapy in ANBL0532 and those receiving radiotherapy in A3973 were similar, with the exception of a significantly higher percentage of patients receiving subsequent immunotherapy in ANBL0532 compared with A3973 (Tables 1 and 2; Appendix Table A1, online only).

Outcomes for the Full Cohort Receiving Radiotherapy

Five-year CILPs were 11.2% ± 1.8% and 7.1% ± 1.4% for all patients receiving radiotherapy in ANBL0532 and A3973, respectively ($P = .0590$; Fig 2A). In contrast, EFS and OS rates were significantly higher for ANBL0532 (5-year EFS and OS rates were 56.2% ± 3.4% and 68.4% ± 3.2%, respectively) compared with A3973 (47.0% ± 3.5% [$P = .0090$] and 57.4% ± 3.5% [$P = .0088$], respectively; Figs 2B and 2C). Similar to findings by Braunstein et al,[16] we found no differences in CILP, EFS, or OS for patients in ANBL0532 when stratified by percentage of LNC using cutoffs of 10%, 15%, and 20% (Appendix Tables A2 and A3, online only).

Of note, 32 and 33 patients in ANBL0532 had major and minor deviations from protocol radiotherapy, respectively (Appendix Table A4, online only). CILP, EFS, and OS did not differ for patients receiving radiotherapy in ANBL0532 with major deviations compared with those without major deviations ($P > .05$). Compared with all patients receiving radiotherapy in A3973, CILP was not different for patients receiving radiotherapy in ANBL0532 without major deviations ($P = .1021$; Appendix Table A5, online only).

Secondary malignancies were seen in 4 patients who received radiotherapy in ANBL0532 (1 in primary radiation field) compared with 5 patients who received radiotherapy in A3973 (3 in primary radiation field; Appendix Tables A6 and A7, online only).

Outcomes for Patients With Incomplete Resection

ANBL0532 included 133 patients with incomplete resection confirmed by central imaging review, whereas A3973 included 47 patients with incomplete resection determined by assessment at time of surgery. Using intention-to-treat analysis, CILP, EFS, and OS were not significantly different between patients with gross residual tumor who received boost radiotherapy in ANBL0532 and patients with gross residual tumor who did not receive boost radiotherapy in A3973 (Fig 3).

We also compared outcomes of 133 patients with incomplete resection with those of 190 patients with complete resection in ANBL0532. CILP was lower in patients with complete resection, with a trend toward significance ($P = .0750$), but no differences in EFS and OS were observed between groups (Appendix Table A8, online only).

ANBL0532 demonstrated improved EFS in patients randomly assigned to tandem SCT, and patients in A3973 only received single SCT.[5,17] We therefore assessed outcomes of patients who were randomly assigned or assigned to receive single SCT and received boost radiotherapy in ANBL0532 (n = 74), with 5-year CILP, EFS, and OS rates of 16.3% ± 4.3%, 50.9% ± 7.0%, and 68.1% ± 6.7%, respectively (Fig 4). In comparison, 5-year CILP, EFS, and OS rates for A3973 patients with incomplete resection and radiotherapy (n = 47) were 10.6% ± 4.6% ($P = .4126$), 48.9% ± 10.1% ($P = .5084$), and 56.9% ± 10.0% ($P = .2835$), respectively (Fig 4). In addition, CILP did not differ between patients who received boost radiotherapy after single SCT and tandem SCT in ANBL0532 ($P > .05$).

Immunotherapy and Cumulative Incidence of Metastatic Progression

A higher proportion of patients in ANBL0532 received immunotherapy compared with A3973 (Tables 1 and 2) and previous studies demonstrated immunotherapy and isotretinoin improve EFS and OS compared with isotretinoin alone.[17,19] Given that CILP was increased in all patients receiving radiotherapy in ANBL0532 compared with those in A3973, with a trend toward significance, we next explored if immunotherapy improved control of distant metastatic disease such that there was decreased competing risk for CILP analyses. Five-year CIMP rates for all patients receiving radiotherapy in ANBL0532 (n = 323) and A3973 (n = 328) were 36.0% ± 2.7% and 45.3% ± 2.8%, respectively ($P = .0158$). Furthermore, 5-year CILP and CIMP rates for patients who received radiotherapy in ANBL0532 and subsequently received immunotherapy (n = 252) were 7.6% ± 1.7% and 31.8% ± 3.0%, respectively, compared with 23.9% ± 5.1% ($P < .0001$) and 50.8% ± 6.0% ($P = .0003$) for those who received radiotherapy in ANBL0532 and subsequently did not receive immunotherapy (n = 71), respectively. Finally, analysis of patients who received immunotherapy after single SCT and radiotherapy in ANBL0532 and patients who received immunotherapy after radiotherapy in A3973 showed no difference in EFS or OS (Appendix Table A9, online only).

DISCUSSION

Locoregional relapse remains an important contributor to treatment failure in high-risk neuroblastoma despite multimodal therapy, including radiotherapy.[6-9] Here, we report practice-changing findings that CILP was not improved in ANBL0532 despite radiation dose escalation with a boost of 14.4 Gy to gross residual tumor compared with the historical A3973 cohort. To our knowledge, this is the largest and only prospective study to have a preplanned analysis of boost radiotherapy for patients with high-risk neuroblastoma and gross residual disease. The significant increases in EFS and OS in ANBL0532 compared with A3973 likely resulted from improved systemic therapy with tandem SCT and anti-GD2 immunotherapy.

Few prospective studies have explored radiation dose escalation to improve local control in patients with high-risk neuroblastoma and incomplete resection. Simon et al[15] found similar EFS and OS between patients who

TABLE 1. Demographic and Clinical Characteristics for All Patients Receiving RT in COG ANBL0532 Versus All Patients Receiving RT in COG A3973

Characteristic	No. (%)		
	COG ANBL0532 (n = 323)	COG A3973 (n = 328)	χ^2 *P*[a]
Age at diagnosis, months			.5247
< 18	50 (15.5)	45 (13.7)	
≥ 18	273 (84.5)	283 (86.3)	
INSS stage			.5147[b]
2 or 3	48 (14.9)	49 (14.9)	
4	274 (84.8)	275 (83.8)	
4S	1 (0.3)	4 (1.2)	
MYCN status			.0548
Not amplified	144 (49.8)	162 (57.9)	
Amplified	145 (50.2)	118 (42.1)	
Unknown	34	48	
Histology			.5460
Favorable	13 (4.6)	9 (3.6)	
Unfavorable	270 (95.4)	244 (96.4)	
Unknown	40	75	
Primary site			.7141
Adrenal	141 (43.7)	149 (46.3)	
Abdominal, other	145 (44.9)	131 (40.7)	
Mediastinal	11 (3.4)	14 (4.3)	
Other	26 (8.0)	28 (8.7)	
Unknown	0	6	
Ploidy			.2756
Hyperdiploid	136 (52.9)	134 (48.2)	
Diploid	121 (47.1)	144 (51.8)	
Unknown	66	50	
End-induction response			.6211
CR, VGPR, or PR	301 (93.2)	305 (94.1)	
< PR	22 (6.8)	19 (5.9)	
Unknown	0	4	
Transplantation			NA
Single	175 (54.2)	328 (100.0)	
Tandem	148 (45.8)	0 (0.0)	
Received immunotherapy post transplantation in COG study			< .0001
Yes	252 (78.0)	75 (22.9)	
No	71 (22.0)	253 (77.1)	

Abbreviations: COG, Children's Oncology Group; CR, complete response; INSS, International Neuroblastoma Staging System; NA, not applicable; PR, partial response; RT, radiotherapy; VGPR, very good partial response.

[a]Percentages and *P* values calculated on the basis of patients with known data for the given characteristic, with patients with unknown status not included.

[b]Fisher's exact test used because of small expected cell sample size.

TABLE 2. Demographic and Clinical Characteristics for Patients With Gross Residual Disease in COG ANBL0532 and Patients Who Had Incomplete Resection in COG A3973

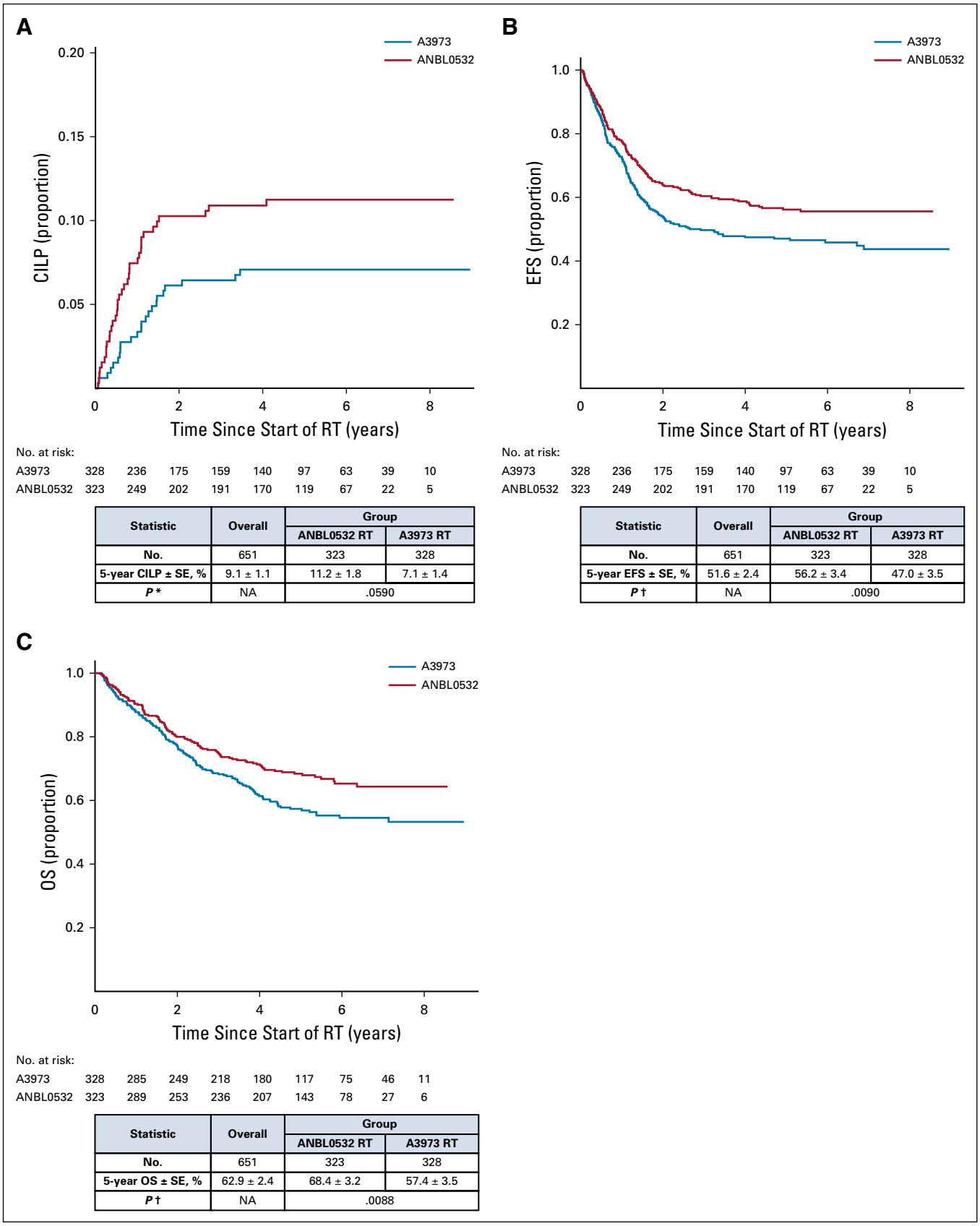
Characteristic	No. (%)			
	COG ANBL0532 Gross Residual Disease			
	Single Transplantation (n = 74)	Tandem Transplantation (n = 59)	COG A3973 Incomplete Resection (n = 47)	χ^2 *P*[a]
Age at diagnosis, months				.7736
< 18	12 (16.2)	7 (11.9)	7 (14.9)	
≥ 18	62 (83.8)	52 (88.1)	40 (85.1)	
INSS stage				.3453[b]
3	16 (21.6)	7 (11.9)	8 (17.0)	
4	58 (78.4)	51 (86.4)	39 (83.0)	
4S	0 (0.0)	1 (1.7)	0 (0.0)	
MYCN status				.4785
Not amplified	41 (58.6)	27 (50.0)	27 (61.4)	
Amplified	29 (41.4)	27 (50.0)	17 (38.6)	
Unknown	4	5	3	
Histology				.3722[b]
Favorable	3 (4.5)	0 (0.0)	1 (2.4)	
Unfavorable	63 (95.5)	51 (100.0)	41 (97.6)	
Unknown	8	8	5	
Primary site				.3979[b]
Adrenal	24 (32.4)	28 (47.5)	17 (37.0)	
Abdominal, other	35 (47.3)	26 (44.1)	23 (50.0)	
Mediastinal	3 (4.1)	2 (3.4)	2 (4.3)	
Other	12 (16.2)	3 (5.1)	4 (8.7)	
Unknown	0	0	1	
Ploidy				.4149
Hyperdiploid	34 (54.8)	30 (62.5)	22 (48.9)	
Diploid	28 (45.2)	18 (37.5)	23 (51.1)	
Unknown	12	11	2	
End-induction response				.0627
CR, VGPR, or PR	68 (91.9)	50 (84.7)	45 (97.8)	
< PR	6 (8.1)	9 (15.3)	1 (2.2)	
Unknown	0	0	1	
Received immunotherapy posttransplantation in COG study				< .0001
Yes	58 (78.4)	40 (67.8)	6 (12.8)	
No	16 (21.6)	19 (32.2)	41 (87.2)	

Abbreviations: COG, Children's Oncology Group; CR, complete response; INSS, International Neuroblastoma Staging System; PR, partial response; VGPR, very good partial response.

[a]Percentages and *P* values calculated on the basis of patients with known data for the given characteristic, with patients with unknown status not included.

[b]Fisher's exact test used because of small expected cell sample size.

received a median radiation dose of 36 Gy (range, 30.6-40 Gy) to residual tumor volume and patients without residual disease after induction chemotherapy. Haas-Kogan et al[2] showed improved local recurrence rates for patients with high-risk neuroblastoma who received 20 Gy of radiation to gross residual disease, including 10 Gy of total-body irradiation (TBI), compared with patients without TBI.

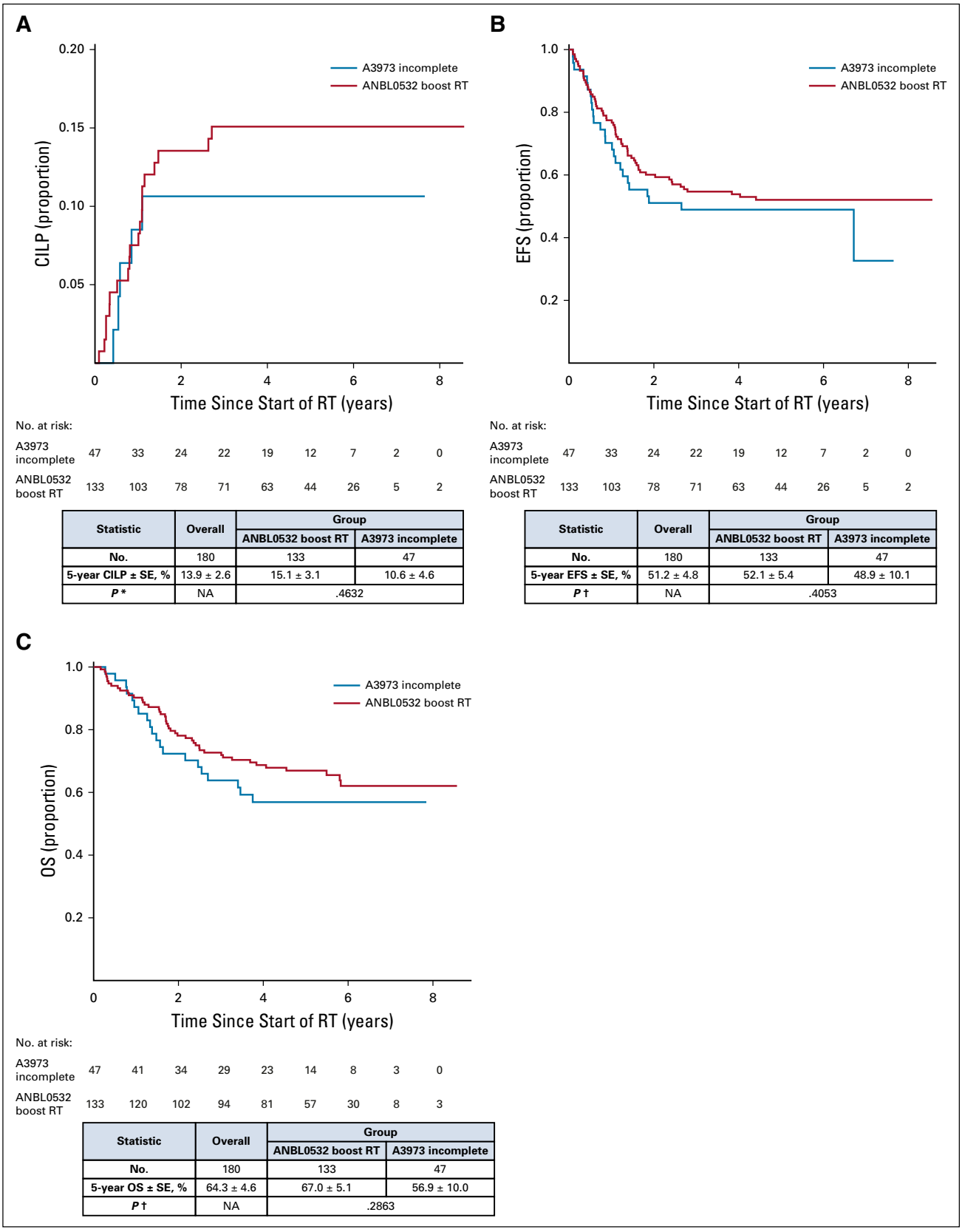


Statistic	Overall	Group	
		ANBL0532 RT	A3973 RT
No.	651	323	328
5-year CILP ± SE, %	9.1 ± 1.1	11.2 ± 1.8	7.1 ± 1.4
P *	NA	.0590	

Statistic	Overall	Group	
		ANBL0532 RT	A3973 RT
No.	651	323	328
5-year EFS ± SE, %	51.6 ± 2.4	56.2 ± 3.4	47.0 ± 3.5
P †	NA	.0090	

Statistic	Overall	Group	
		ANBL0532 RT	A3973 RT
No.	651	323	328
5-year OS ± SE, %	62.9 ± 2.4	68.4 ± 3.2	57.4 ± 3.5
P †	NA	.0088	

FIG 2. (A) Cumulative incidence of local progression (CILP), (B) event-free survival (EFS), and (C) overall survival (OS) for patients receiving radiotherapy (RT) in Children's Oncology Group (COG) ANBL0532 and COG A3973.(*) Grey's test. (†) Log-rank test.

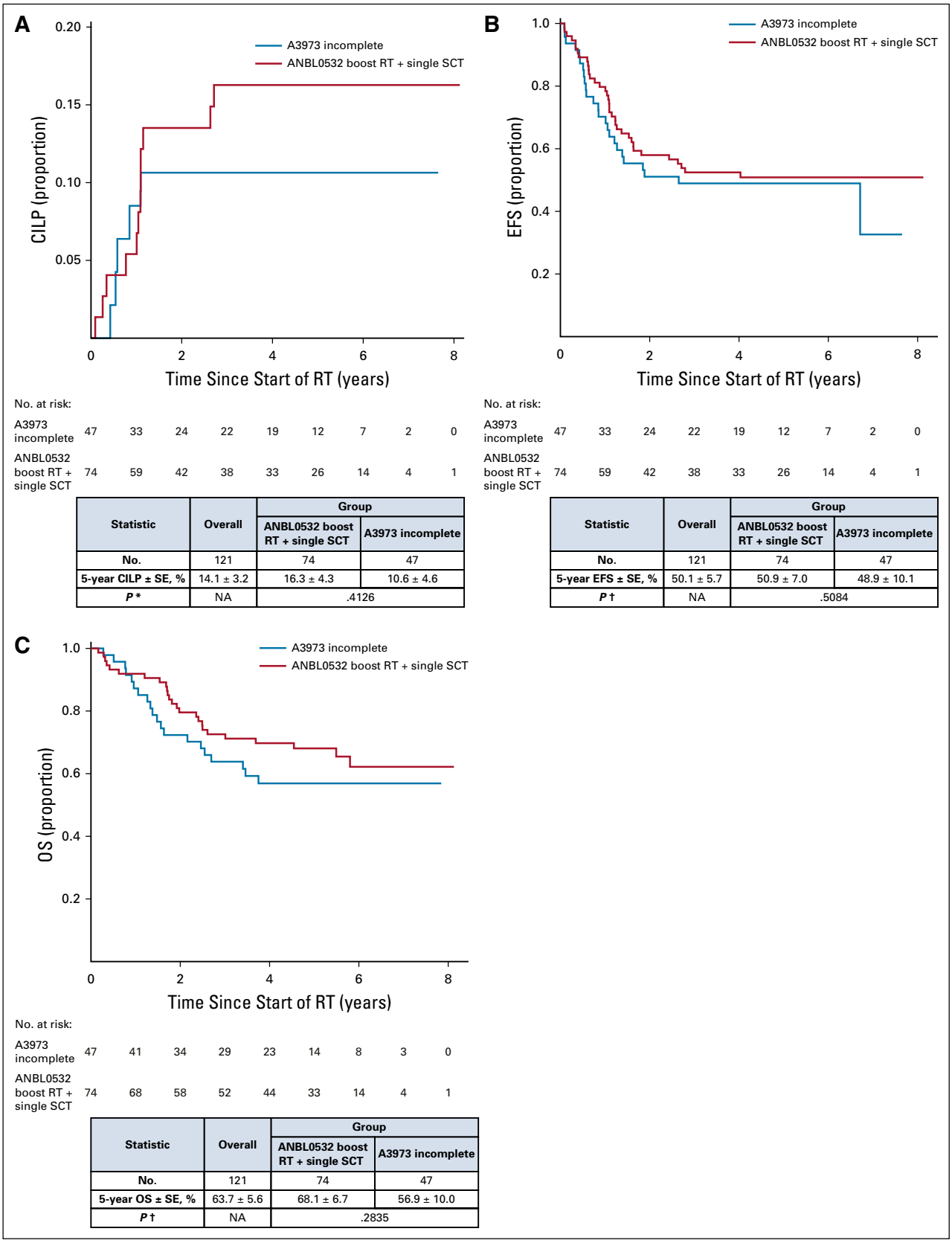


Statistic	Overall	Group	
		ANBL0532 boost RT	A3973 incomplete
No.	180	133	47
5-year CILP ± SE, %	13.9 ± 2.6	15.1 ± 3.1	10.6 ± 4.6
P *	NA	.4632	

Statistic	Overall	Group	
		ANBL0532 boost RT	A3973 incomplete
No.	180	133	47
5-year EFS ± SE, %	51.2 ± 4.8	52.1 ± 5.4	48.9 ± 10.1
P †	NA	.4053	

Statistic	Overall	Group	
		ANBL0532 boost RT	A3973 incomplete
No.	180	133	47
5-year OS ± SE, %	64.3 ± 4.6	67.0 ± 5.1	56.9 ± 10.0
P †	NA	.2863	

FIG 3. (A) Cumulative incidence of local progression (CILP), (B) event-free survival (EFS), and (C) overall survival (OS) for patients who received boost radiotherapy (RT) for gross residual disease in Children's Oncology Group (COG) ANBL0532 and patients who received RT and had ≤ 90% primary tumor resection in COG A3973. (*) Grey's test. (†) Log-rank test.



Statistic	Overall	Group	
		ANBL0532 boost RT + single SCT	A3973 incomplete
No.	121	74	47
5-year CILP ± SE, %	14.1 ± 3.2	16.3 ± 4.3	10.6 ± 4.6
P *	NA	.4126	

Statistic	Overall	Group	
		ANBL0532 boost RT + single SCT	A3973 incomplete
No.	121	74	47
5-year EFS ± SE, %	50.1 ± 5.7	50.9 ± 7.0	48.9 ± 10.1
P †	NA	.5084	

Statistic	Overall	Group	
		ANBL0532 boost RT + single SCT	A3973 incomplete
No.	121	74	47
5-year OS ± SE, %	63.7 ± 5.6	68.1 ± 6.7	56.9 ± 10.0
P †	NA	.2835	

FIG 4. (A) Cumulative incidence of local progression (CILP), (B) event-free survival (EFS), and (C) overall survival (OS) for patients who received single stem-cell transplantation (SCT) and boost radiotherapy (RT) for gross residual disease in Children's Oncology Group (COG) ANBL0532 and patients who received RT and had ≤ 90% primary tumor resection in COG A3973. (*) Grey's test. (†) Log-rank test.

A retrospective single-institution cohort study of patients with high-risk neuroblastoma and subtotal resection found local failure rates of 0% and 30% after ≥ 30 and < 30 Gy (P = .12), respectively.[22] In contrast, another single-institution retrospective study found > 21.6 Gy provided no local relapse-free survival benefit in high-risk neuroblastoma; however, radiation doses for patients with gross residual disease were not specified.[23] Our findings demonstrate no benefit of boost radiotherapy for gross residual disease.

Interestingly, for all patients receiving radiotherapy in ANBL0532, CILP was higher, with a trend toward significance, compared with those receiving radiotherapy in A3973. Radiotherapy plans were centrally reviewed in both studies. Most major deviations in ANBL0532 were either patients with gross residual disease who did not receive boost radiotherapy (n = 20) or patients with complete resection who inappropriately received boost radiotherapy (n = 8). These factors are unlikely to explain increased CILP in ANBL0532. Nonetheless, future trials may benefit from central review of radiotherapy plans before treatment delivery to reduce the number of major deviations. In addition, the percentage of LNC was similar between patients receiving radiotherapy in ANBL0532 and A3973, and no association between LNC and outcome was observed.[16] We found no difference in CILP between patients with incomplete resection receiving tandem or single SCT; therefore, delay in radiotherapy because of tandem SCT is unlikely to contribute to increased CILP.

Although surgical guidelines were consistent between A3973 and ANBL0532, we found higher rates of incomplete resections for patients receiving radiotherapy in ANBL0532 (n = 133) compared with A3973 (n = 47), respectively. Furthermore, there were higher rates of less-than-partial response at end of induction, with a trend toward significance (P = .0627), for patients in ANBL0532 compared with A3973. One potential explanation for this finding is that surgeons knew patients with gross residual disease would receive boost radiotherapy and were therefore less aggressive with surgical resection, thus leading to an increased rate of local failure. Although some studies did not find an association between extent of surgical resection and local control,[24-26] prospective data from A3973 found lower CILP for surgeon-assessed extent of resection ≥ 90%, and major complications were not increased with greater extent of resection.[4] In addition, patients with complete resection had lower CILP, with a trend toward significance, compared with patients with incomplete resection in ANBL0532. Although the differences in extent of resection between the 2 trials may be a confounding factor, our results suggest that boost radiotherapy and tandem SCT cannot compensate for incomplete resection. Attempts to achieve ≥ 90% resection may be important for local control; however, this study was not designed to provide a definitive answer regarding aggressive resection.

A higher percentage of patients who received radiotherapy in ANBL0532 subsequently received immunotherapy compared with patients in A3973 (Tables 1 and 2; Appendix Table A1). Post hoc analysis found that anti-GD2 immunotherapy decreased both locoregional and distant failure; however, patients in ANBL0532 who did not subsequently receive immunotherapy included those who experienced disease progression prior to postconsolidation therapy. In addition, anti-GD2 immunotherapy did not lead to decreased competing risk of metastatic progression as first event for CILP analyses. Therefore, the increased proportion of patients in ANBL0532 receiving immunotherapy is also unlikely to explain the higher rates of locoregional relapse.

Future studies will be important to examine additional strategies to improve locoregional control. For example, ANBL09P1 was a pilot study examining the safety of ^{131}I- MIBG during induction therapy for high-risk neuroblastoma, and ANBL1531 is an ongoing phase III clinical trial investigating whether ^{131}I-MIBG improves EFS in patients with MIBG-avid tumors (ClinicalTrials.gov identifier: NCT03126916). In addition, the role of radiosensitizers, such as histone deacetylase and DNA-dependent protein kinase inhibitors, in controlling local relapse warrants further investigation.[27-31] Finally, because imaging at first relapse was not available for this study, future studies are needed to explore whether local progression occurs within the radiation field and, if not, identify areas at high risk of locoregional relapse that could benefit from radiotherapy.

Our study benefits from its prospective design, large size for this rare disease, and use of central radiology and radiotherapy reviews. Nevertheless, we acknowledge certain limitations of our analysis, such as use of a historical control and small numbers of local recurrences. Use of historical controls can lead to confounding factors, including shifts in clinical practice over time, such as adoption of intensity-modulated radiotherapy and proton therapy, or potential interactions between changes in treatment regimens. Definitions of incomplete resection differed between the 2 trials, with ANBL0532 using central radiology review and A3973 using surgical assessment. However, limited concordance between central imaging review and surgical review of incomplete resection may have contributed to differences in sample size between the 2 trials.[4] In the future, using imaging definitions of incomplete resection or response to induction therapy may produce more consistent criteria for comparisons. Furthermore, von Allmen et al[4] reported 5-year CILP of 19.8% for 66 patients with < 90% resection in A3973; however, only 46 of those patients received radiotherapy during the study, suggesting some patients with incomplete resection experienced disease progression between the time of surgery and radiotherapy, and a more favorable group of patients with incomplete resection received radiotherapy in A3973. Despite the small number of patients with events, CILP was higher in

ANBL0532; therefore, even with a larger sample size, it is unlikely that boost radiotherapy would be shown to significantly improve local control.

Since the initiation of ANBL0532, most institutions have considered this protocol and inclusion of boost radiotherapy as standard of care for high-risk neuroblastoma. Before data from ANBL0532 matured for analysis, the current high-risk neuroblastoma protocol ANBL1531 incorporated boost radiotherapy into its study design. Within the pediatric oncology community, it is often commonplace to treat per prior protocol guidelines even if the patient is not enrolled in the clinical trial. Nonetheless, caution should be used when treating using guidelines not yet supported by evidence from prior studies.[32] Although the risks of boost radiotherapy were likely limited given the small gross residual tumor volume in most cases, exposure to higher-dose radiation without demonstrable benefit is to be avoided in this vulnerable population.

In conclusion, we demonstrate that boost radiotherapy to gross residual disease does not improve local control, and this strategy is not recommended. Furthermore, aggressive local resection remains important for patients with high-risk neuroblastoma. New therapeutic strategies are needed to address locoregional failure in high-risk neuroblastoma.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Prospective Evaluation of Radiation Dose Escalation in Patients With High-Risk Neuroblastoma and Gross Residual Disease After Surgery: A Report From the Children's Oncology Group ANBL0532 Study

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APPENDIX

TABLE A1. Demographic and Clinical Characteristics for All Patients With End-Induction CR Receiving RT in COG ANBL0532 Versus All Patients With End-Induction CR Receiving RT in COG A3973

Characteristic	No. (%)		
	COG ANBL0532 (n = 72)	COG A3973 (n = 88)	χ^2 *P*[a]
Age at diagnosis, months			.8740
< 18	10 (13.9)	13 (14.8)	
≥ 18	62 (86.1)	75 (85.2)	
INSS stage			.4005[b]
2 or 3	18 (25.0)	22 (25.0)	
4	54 (75.0)	63 (71.6)	
4S	0 (0.0)	3 (3.4)	
MYCN status			.6214
Not amplified	25 (40.3)	36 (44.4)	
Amplified	37 (59.7)	45 (55.6)	
Unknown	10	7	
Histology			.6718[b]
Favorable	3 (4.6)	2 (2.8)	
Unfavorable	63 (95.5)	69 (97.2)	
Unknown	6	17	
Primary site			.5017
Adrenal	27 (37.5)	34 (40.0)	
Abdominal, other	40 (55.6)	41 (48.2)	
Mediastinal	3 (4.2)	3 (3.5)	
Other	2 (2.8)	7 (8.2)	
Unknown	0	3	
Ploidy			.4294
Hyperdiploid	29 (51.8)	35 (44.9)	
Diploid	27 (48.2)	43 (55.1)	
Unknown	16	10	
Transplantation			NA
Single	39 (54.2)	88 (100.0)	
Tandem	33 (45.8)	0 (0.0)	
Received immunotherapy posttransplantation in COG study			< .0001
Yes	61 (84.7)	18 (20.5)	
No	11 (15.3)	70 (79.5)	

Abbreviations: COG, Children's Oncology Group; CR, complete response; INSS, International Neuroblastoma Staging System; NA, not applicable; RT, radiotherapy.

[a]Percentages and *P* values calculated on the basis of patients with known data for the given characteristic, with patients with unknown status not included.

[b]Fisher's exact test used because of small expected cell sample size.

TABLE A2. Five-Year CILP, EFS, and OS by Percentage of LNC Using Cutoffs of 10%, 15%, and 20% (n = 323): Method A (average)

LNC (%)	No. (%)	CILP ± SE (%)	*P*[a]	EFS ± SE (%)	*P*[b]	OS ± SE (%)	*P*[b]
Cutoff 1			.4247		.6113		.1705
< 10	51 (15.8)	7.8 ± 3.8		58.4 ± 8.0		78.4 ± 6.9	
≥ 10	272 (84.2)	11.9 ± 2.0		55.7 ± 3.8		66.5 ± 3.6	
Cutoff 2			.4918		.9939		.7615
< 15	125 (38.7)	9.6 ± 2.6		55.8 ± 5.3		70.5 ± 4.9	
≥ 15	198 (61.3)	12.3 ± 2.4		56.4 ± 4.5		67.1 ± 4.3	
Cutoff 3			.2612		.6630		.8510
< 20	198 (61.3)	9.7 ± 2.1		55.0 ± 4.3		68.8 ± 4.0	
≥ 20	125 (38.7)	13.7 ± 3.1		58.1 ± 5.7		67.8 ± 5.4	

Abbreviations: CILP, cumulative incidence of progression; EFS, event-free survival; LNC, lymph node coverage; OS, overall survival.
[a]Gray's test.
[b]Log-rank test.

TABLE A3. Five-Year CILP, EFS, and OS by Percentage of LNC Using Cutoffs of 10%, 15%, and 20% (n = 323): Method B (primary site)

LNC (%)	No. (%)	CILP ± SE (%)	*P*[a]	EFS ± SE (%)	*P*[b]	OS ± SE (%)	*P*[b]
Cutoff 1			.2870		.1749		.6788
< 10	15 (4.6)	20.0 ± 10.9		40.0 ± 15.5		73.3 ± 14.3	
≥ 10	308 (95.4)	10.8 ± 1.8		57.0 ± 3.5		68.1 ± 3.3	
Cutoff 2			.4785		.8923		.1777
< 15	26 (8.0)	15.4 ± 7.3		57.7 ± 12.5		80.8 ± 9.8	
≥ 15	297 (92.0)	10.9 ± 1.8		56.0 ± 3.5		67.3 ± 3.4	
Cutoff 3			.4785		.8923		.1777
< 20	26 (8.0)	15.4 ± 7.3		57.7 ± 12.5		80.8 ± 9.8	
≥ 20	297 (92.0)	10.9 ± 1.8		56.0 ± 3.5		67.3 ± 3.4	

Abbreviations: CILP, cumulative incidence of progression; EFS, event-free survival; LNC, lymph node coverage; OS, overall survival.
[a]Gray's test.
[b]Log-rank test.

TABLE A4. Dose and Volume Deviations for COG ANBL0532

Deviation	Dose	Volume
Major (n = 32)	Prescribed dose differs from that in protocol by > 10%	Portion of tumor (GTV) or potentially tumor-bearing area (CTV) is not included in treated volume
No.	(n = 30)	(n = 26)
Minor (n = 33)	Prescribed dose differs from that in protocol by between 6% and 10%; entire PTV is not encompassed within isodose surface representing 95% of prescription dose, or > 10% of PTV receives > 110% of prescription dose for 3D conformal and IMRT treatments, or dose variation in treated volume shall be within +7% and −5% of the prescription point dose for 2D treatments; or critical structure dose limits are exceeded by < 10%	Margins less than specified or fields excessively large as deemed by study reviewer
No.	(n = 31)	(n = 3)

Abbreviations: COG, Children's Oncology Group; CTV, clinical target volume; D, dimensional; GTV, gross tumor volume; IMRT, intensity-modulated radiotherapy; PTV, planning target volume.

TABLE A5. Five-Year CILP, EFS, and OS Between All Patients Receiving RT Without Major Deviations in ANBL0532 and All Patients Receiving RT in A3973

RT	CILP ± SE (%)	*P*[a]	EFS ± SE (%)	*P*[b]	OS ± SE (%)	*P*[b]
All		.1021		.0065		.0043
Without major deviations in ANBL0532 (n = 291)	10.7 ± 1.8		56.7 ± 3.6		69.7 ± 3.3	
In A3973 (n = 328)	7.1 ± 1.4		47.0 ± 3.5		57.4 ± 3.5	

Abbreviations: CILP, cumulative incidence of progression; EFS, event-free survival; OS, overall survival; RT, radiotherapy.
[a]Gray's test.
[b]Log-rank test.

TABLE A6. Events for All Patients Receiving RT in COG A3973 and COG ANBL0532

Event	No. (%)	
	A3973 (n = 328)	ANBL0532 (n = 323)
Local	8 (4.5)	13 (9.3)
Local plus metastatic	15 (8.5)	23 (16.4)
Metastatic	133 (75.6)	92 (65.7)
Unknown relapse/PD	3 (1.7)	0 (0.0)
Death as first event	12 (6.8)	8 (5.7)
Any SMN	5 (2.8)	4 (2.9)
Solid SMN	4 (2.3)	4 (2.9)
	Soft tissue sarcoma, malignant fibrous histiocytoma, osteosarcoma, renal cell carcinoma, small blue cell tumor	Glioblastoma, thyroid minimally invasive follicular carcinoma, spindle cell sarcoma, thyroid papillary carcinoma
In–RT primary field SMN	3 (1.7)	1 (0.7)
	Soft tissue sarcoma, malignant fibrous histiocytoma, osteosarcoma, renal cell carcinoma	Spindle cell sarcoma

Abbreviations: COG, Children's Oncology Group; PD, progressive disease; RT, radiotherapy; SMN, secondary malignant neoplasm.

TABLE A7. Events for Patients Who Had Incomplete Resection and Received 21.6 Gy in COG A3973 and Patients Who Received Boost RT in COG ANBL0532

Event	No. (%)		
		ANBL0532 Boost RT	
	A3973 (n = 47)	Single SCT (n = 74)	Tandem SCT (n = 59)
Local	0 (0.0)	5 (13.9)	1 (3.7)
Local plus metastatic	5 (20.0)	7 (19.4)	7 (25.9)
Metastatic	17 (68.0)	22 (61.1)	17 (63.0)
Unknown relapse/PD	0 (0.0)	0 (0.0)	0 (0.0)
Death as first event	1 (4.0)	1 (2.8)	1 (3.7)
Any SMN	2 (8.0)	1 (2.8)	1 (3.7)
Solid SMN	2 (8.0)	1 (2.8)	1 (3.7)
	Soft tissue sarcoma, small blue cell tumor	Thyroid papillary carcinoma	Thyroid minimally invasive follicular carcinoma
In–RT primary field SMN	1 (4.0)	0 (0.0)	0 (0.0)
	Soft tissue sarcoma		

Abbreviations: COG, Children's Oncology Group; PD, progressive disease; RT, radiotherapy; SMN, secondary malignant neoplasm.

TABLE A8. Five-Year CILP, EFS, and OS Between All Patients Receiving RT After Complete Resection Versus Incomplete Resection in ANBL0532

RT	CILP ± SE (%)	*P*[a]	EFS ± SE (%)	*P*[b]	OS ± SE (%)	*P*[b]
All		.0750		.2388		.5137
With complete resection (n = 190)	8.5 ± 2.0		59.1 ± 4.4		69.4 ± 4.1	
With incomplete resection (n = 133)	15.1 ± 3.1		52.1 ± 5.4		67.0 ± 5.1	

Abbreviations: CILP, cumulative incidence of progression; EFS, event-free survival; OS, overall survival; RT, radiotherapy.
[a]Gray's test.
[b]Log-rank test.

TABLE A9. Five-Year EFS and OS Between All Patients Receiving Subsequent Immunotherapy in Trial After Single SCT and RT in ANBL0532 and A3973

Immunotherapy	EFS ± SE (%)	*P*[a]	OS ± SE (%)	*P*[a]
All		.1760		.4333
After single SCT and RT in ANBL0532 (n = 144)	53.5 ± 5.0		68.6 ± 4.7	
After SCT and RT in A3973 (n = 75)	45.3 ± 7.7		62.3 ± 7.7	

Abbreviations: EFS, event-free survival; OS, overall survival; RT, radiotherapy; SCT, stem-cell transplantation.
[a]Log-rank test.