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Role of Extent of Prophylactic Regional Lymph Node Radiotherapy on Survival in High Risk Neuroblastoma: A Report from the COG A3973 Study

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Abstract

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CONFLICT OF INTEREST STATEMENT

Authors SB, WL, SK, JV, AD, KD, RC, KM, LD, KM, SC, BS, DVA, MP, CVR, JP, MLQ, and DHK have no relevant disclosures.

Purpose—Neuroblastoma is the most common extracranial solid pediatric malignancy, with poor outcomes in high-risk disease. Standard treatment approaches employ an increasing array of aggressive multimodal therapies of which local control with surgery and radiotherapy remains a backbone; however, the benefit of broad regional nodal irradiation remains controversial. We analyzed centrally reviewed radiation therapy data from patients enrolled on COG A3973 to evaluate the impact of primary site irradiation and extent of regional nodal coverage stratified by extent of surgical resection.

Methods—330 high-risk neuroblastoma patients with centrally reviewed radiotherapy plans were analyzed. Outcome was evaluated by the extent of nodal irradiation. For the 171 patients who also underwent surgery (centrally reviewed), outcome was likewise analyzed according to the extent of resection. Overall survival (OS), event-free survival (EFS) and cumulative incidence of local progression (CILP) were examined by Kaplan-Meier, log-rank test (EFS, OS), and Grey's test (CILP).

Results—The 5-yr CILP, EFS, and OS for all 330 patients receiving radiotherapy on A3973 were 8.5±1.5%, 47.2±3.0%, and 59.7±3.0%, respectively. There were no significant differences in outcomes based on extent of lymph node irradiation regardless of the degree of surgical resection (<90% or ≥90%).

Conclusion—While local control remains a significant component of treatment of high-risk neuroblastoma, our results suggest there is no benefit of extensive lymph node irradiation, irrespective of the extent of surgical resection preceding stem cell transplant.

Keywords

neuroblastoma; radiotherapy; lymph nodes; high-risk

INTRODUCTION

Over recent decades, treatment of patients with high-risk neuroblastoma has been characterized by an increasingly intensified multimodal approach due to historically poor outcomes, with 5-year survival of less than 50% [1–4]. Local relapse remains a common failure pattern in high-risk disease, emphasizing the importance of surgery and radiation [1, 5–9].

COG A3973 was a randomized study that enrolled 486 high-risk neuroblastoma patients between 2/9/2001 and 3/31/2006 evaluating the effect of immunomagnetic bead purging peripheral blood stem cells (PBSC) on outcome following myeloablative chemotherapy and autologous stem cell transplantation (ASCT). Five-year event-free survival (EFS) and overall survival (OS) were 38±4% and 50±4.5%, respectively (n=486). There was no benefit observed for purging of PBSC for ASCT [10].

Analyses of prior cooperative group studies support the role of dose-escalated radiotherapy towards improved outcomes. Haas-Kogan et al. reported improved local control among high-risk patients treated on CCG 3891 who received 10 Gy total body irradiation, in addition to the standard 10 Gy tumor-bed directed radiotherapy for gross residual disease (5-yr local relapse [LR] 22% vs 52%, respectively)[1]. Likewise, smaller institutional series have

reported improved outcomes with escalation of locoregional radiation regimens [9, 11–13]. Therefore, for COG A3973, primary site radiation was increased to 21.6 Gy without TBI and radiation targets included the volume of tumor remaining prior to attempted surgical resection, as defined by CT, MRI, +/− MIBG scans. Although uninvolved draining regions were not explicitly covered, many radiation oncologists included such prophylactic nodal irradiation due to a widely held conception that such coverage improves local control and clinical outcome. In this report of COG A3973, we analyze the effects of adjuvant radiotherapy to the primary site on EFS, OS, and the cumulative incidence of local progression (CILP). We further determined the influence of prophylactic lymph node irradiation on EFS, OS and CILP.

PATIENTS AND METHODS

Radiotherapy to the primary site, given after ASCT, was prescribed to all patients regardless of extent of resection and consisted of 21.6 Gy in 1.8 Gy per daily fractions to the post-induction chemotherapy, pre-operative tumor volume. Per protocol radiotherapy was directed to the primary tumor site and residual soft-tissue disease following ASCT prior to attempted surgical resection. Of the 486 patients treated on COG A3973, 156 did not receive radiation, were ineligible, or did not have data submitted for review. 339 patients had radiotherapy plans and associated diagnostic scans, operative reports, and clinical data for further evaluation. Of the 339, 7 did not have percent lymph node coverage (LNC) data and 2 were subsequently deemed ineligible for A3973, yielding the 330 patient analytic cohort (Figure 1). Central review of the extent of lymph node coverage and radiation to primary tumor and other sites was performed on all 330 patients. Lymph node coverage was assessed by review of radiation ports and scored as estimated percent coverage for each of four nodal stations: cervical, mediastinal, para-aortic, and pelvic [14]. Of the 330 patients, extent of resection (≥ 90% vs <90%) was assessed by the surgeon at the time of resection and confirmed by central review in 171 patients; this cohort of n=171 is hereafter referred to as the “radiation/surgery central review cohort” (Figure 1). Examples of extent of lymph node irradiation as derived from patient radiation ports are shown in Supplemental Figure 1. The primary site dose and field of radiotherapy was not adjusted for extent of resection.

Statistical Considerations

LNC was estimated in four anatomical regions [para-aortic (PA), pelvic (P), mediastinal (M), cervical (C)], and the per-patient average percentage of LNC was calculated using two different approaches. Approach A weighted all regions equally, and Approach B assessed only the lymph node region that conformed to the location of the primary tumor. For example, if LNCs for an adrenal primary tumor were PA=100%, P=0%, M=50%, C=0%, Approach A yields (100%+0%+50%+0%)/4 = 37.5% average LNC, whereas Approach B yields 100% LNC (as only the PA lymph node region was considered for an adrenal primary tumor). Approach A was used throughout this manuscript unless otherwise stated.

The proportions of patients above and below the median of the average percent LNC were calculated as were the frequencies of major and minor deviations/violations during radiation therapy. The radiation cohort was repeatedly dichotomized using the first, second, and third

quartile of average percent LNC. Note that ties may occur at the median value, resulting in unequal sample size above and below the median. Analyses comparing subgroups by average percent LNC were repeated within the centrally reviewed surgical subgroup and then further stratified by extent of primary tumor resection (≥90% vs <90%). Comparisons were made for patients with versus without radiation deviations/violations.

Per protocol, post-induction complete response (CR) on imaging was defined as no evidence of primary tumor and no evidence of metastases. A partial response (PR) was defined as a 50–90% reduction in primary tumor and ≥ 50% reduction in measurable sites of metastatic disease.

EFS time was calculated from study enrollment until first occurrence of relapse, progressive disease, secondary malignancy, death from any cause, or until last contact if no event occurred. For OS, time to event was calculated from study enrollment until death from any cause or until last contact with the patient. For CILP, time was calculated from study enrollment until first occurrence of the event of interest (progressive disease at the primary site) or a competing risk (relapse or progressive disease at a non-primary site, secondary malignancy, or death from any cause), or until last contact with the patient if no event or competing risk occurred. For EFS and OS, survival probabilities were computed using the Kaplan-Meier method with standard errors according to the methods of Peto and subgroups were compared using the log-rank test (Figure 2A). CILP estimates were computed and compared between subgroups using Gray's test (Figure 2B). Multivariable models of EFS, OS, and CLIP were used to investigate potential interactions of the prognostic contribution of average percent LNC with *MYCN* status, or with treatment with immunotherapy, using time-dependent covariates to make adjustment for non-proportional hazards if necessary.

Analyses were performed using SAS® version 9.2 (SAS Institute Inc, Cary, NC) and R (The R Project for Statistical Computing, Vienna, Austria; https://www.r-project.org/). *P* values less than 0.05 were considered statistically significant.

RESULTS

Characteristics of patient cohort

Of the 330 patients, a majority presented at age ≥18 months (n=285; 86%) (Table 1). Based on International Neuroblastoma Staging System (INSS) criteria [15], the disease was categorized as stage 4 in 277 (84%) patients, stage 4S in 4 (1%), and either stage 2 or 3 in the remaining 49 (14%) patients. *MYCN* was amplified in 118 (42%) of 282 patients for whom *MYCN* status was known, and histology was considered unfavorable in 246 (96%) of 255 patients with available histologic data. Of 280 patients with known DNA ploidy, 145 (52%) had diploid tumors. Patients who received <20% average LNC were similar to those who received ≥20% average LNC in terms of baseline characteristics, except for end induction response. Of those who received <20% LNC, 60% were CR or PR at the end of induction, compared to only 34% CR/PR who received ≥20% LNC (p=0.02) (Table 1). There was no evidence of an association of percentage of LN coverage with *MYCN* status (p=0.4) or treatment with immunotherapy (p=0.2). Of the 171 patients in the radiation/surgery central review cohort, 125 had >90% resection.

Extent of lymph node coverage and survival

The 5-year CILP, EFS, and OS rates for all 330 patients receiving radiotherapy on A3973 were 8.5±1.5%, 47.2±3.0%, and 59.7±3.0%, respectively (Figure 2). The first, second, and third quartiles of percent LNC for this cohort were 10%, 15%, and 20%, respectively (using Approach A described in the Statistical Considerations section above). There were 197 (60%) patients with average percent LNC at or above the median, and 133 (40%) below; 265 (80%) patients with average percent LNC at or above the first quartile, and 65 (20%) below; 113 (34%) patients with average percent LNC at or above the third quartile, and 217 (66%) below. Regardless of which cut-off was selected to discriminate low versus high average percent LNC, there were no statistically significant differences in EFS, OS, or CILP in the overall cohort (Supplemental Table 1, Figure 3). Moreover, the absolute differences in CILP, EFS or OS at 5 years between the low vs high LNC patient cohorts were small, ranging from 0.3% to 6.5%.

The results were similar if Approach B was used to calculate the average percent LNC. The quartiles of percent LNC were 40%, 60%, and 80%. There were 182 (55%) patients with average percent LNC at or above the median, and 148 (45%) below; 255 (77%) patients with average percent LNC at or above the first quartile, and 75 (23%) below; 91 (26%) patients with average percent LNC at or above the third quartile, and 239 (74%) below. Regardless of which cut-off was selected to discriminate low versus high average percent LNC (via Approach B), there were no statistically significant differences in EFS, OS, or CILP in the overall cohort (data not shown). *MYCN* status was statistically significant in univariate models for EFS and OS, but not CLIP. Treatment with immunotherapy was not statistically significantly prognostic of EFS, OS, or CLIP in univariate models. Average percent LNC remained non-significant in multivariable models of EFS, OS, and CLIP regardless of inclusion of *MYCN* status, immunotherapy treatment, or interactions terms of average percent LNC with *MYCN* status or immunotherapy treatment.

Of note, there were 17 (5%) patients with major deviations during radiation therapy and 54 (16%) patients with minor deviations (Supplemental Table 2). No statistically significant differences in EFS, OS, or CILP were observed between patient groups when stratified by presence versus absence of deviations (data not shown).

For the 171 patients in the radiation/surgery central review cohort, the 5-year EFS, OS, and CILP rates were 50.2%±4.2%, 62.2%±4.0%, and 9.4%±2.2%, respectively (Supplemental Table 3, Figure 4). Within the subset that had ≥90% resection (n=125), EFS, OS, and CILP were similar regardless of which cut-off was selected to discriminate low versus high average percent lymph node coverage (Supplemental Table 3, Figure 5). The same was true within the subset of patients with <90% resection (n=46) (Supplemental Table 3).

DISCUSSION

Survival in high-risk neuroblastoma patients has continually improved in recent eras, attributed to intensification in therapeutic approaches, for which aggressive local control including adjuvant primary tumor-bed directed radiotherapy regardless of response of the primary to chemotherapy or the extent of surgical resection remains a backbone of treatment

However, survival in high-risk patients remains less than 50% despite these improvements [4].

Current high-risk neuroblastoma treatment approaches incorporate 5–6 cycles of induction chemotherapy, followed by surgery, consolidation with high-dose chemotherapy with autologous hematopoietic stem cell rescue, and post-consolidation treatment with immunotherapy (anti-GD2 monoclonal antibody), cytokines (GM-CSF and IL-2), and isotretinoin. Focal radiation to the primary site and any residual metastatic sites is given after transplant and before post consolidation therapy [16]. This study demonstrates no statistically significant benefit in a larger extent of prophylactic lymph node irradiation on local progression or overall survival. Moreover, extended lymph node coverage lacked benefit regardless of extent of surgical resection.

Of note, our study cohort (n=330) appears to have a slightly better survival rate than the overall A3973 cohort (n=486). This is not surprising, given that our subset of 330 patients was selected because they had received XRT, and to receive XRT, patients must have completed induction therapy without progression. Any comparison of those who did versus did not receive XRT is therefore biased. The appearance of superior outcome in those who received XRT should not be considered evidence for concluding that the addition of XRT leads to superior outcome.

Notably, radiotherapy is implicated in numerous late toxicities of multimodal neuroblastoma treatment including impairment in musculoskeletal growth, fertility, and cardiopulmonary function, as well as endocrinopathies, bladder dysfunction, poor psychosocial health, and secondary malignancies [17, 18]. Radiation fields covering prophylactic nodal stations are by definition larger than fields encompassing gross disease alone and therefore, confirming lack of benefit for such extended fields will likely limit future radiation-associated toxicities. Therefore this current analysis supports restricting treatment volumes to the primary tumor bed and involved lymph nodes to 21.6 Gy without inclusion of uninvolved regional lymph node stations. Moreover, the lack of difference in outcomes by extent of resection with surgery plus RT supports abrogating pursuit of extensive, morbid surgeries in pursuit of prophylactic uninvolved lymph node dissection. These findings thus reinforce surgical guidelines of COG A3973 and current protocols that recommend attempt at definitive resection of the primary tumor and involved regional lymph nodes but not removal of grossly normal lymphatic echelons. The completed Children’s Oncology Group Phase 3 trial, ANBL0532, will allow analysis of the role of an additional radiotherapy boost for those high-risk patients who fail to achieve a gross total resection. In the current era, a boost to a total dose of 3600 cGy is commonly employed in the setting of gross disease, but was not standard of care in the era of A3973. In our analysis, the lack a boost to 3600 cGy thus diminishes the potential confounder of incidental dose to regional lymph nodes within the “fall off” gradient outside of the primary target. Treatment in the modern era with techniques including IMRT and proton radiotherapy allow for even greater uninvolved tissue sparing, possibly leading to decreased toxicity without sacrifice of locoregional control [19, 20]. Simon et al. delivered doses of 30.6–40 Gy to relatively small volumes of residual primary tumor and found that these higher radiation doses appeared to compensate for the disadvantage of incomplete response to induction chemotherapy [13]. Acute and late side

effects were limited, albeit with a median follow-up time of only 3.6 years (range 0.6–8.0 years).

Ultimately, refinements in risk classification emerging from greater understanding of molecular features may lead to precision-based targeted therapies. However, current experimental approaches employing more aggressive systemic therapies including cytotoxic chemotherapies (*e.g.* topotecan), novel immunotherapy and radiopharmaceuticals (*e.g.* ^{131}I-MIBG) will continue to warrant judicious use of local therapies to further diminish local failures [16, 21].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the Children's Oncology Group. Restrictions apply to the availability of these data.

Abbreviations

OS	Overall survival
EFS	Event-free survival
CILP	Cumulative incidence of local progression
PBSC	Peripheral blood stem cell
ASCT	Autologous stem cell transplant
TBI	Total body irradiation
LNC	Lymph node coverage
XRT	External beam radiotherapy

REFERENCES

1. 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 2003; 56: 28–39. [PubMed: 12694821]
2. 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 2009; 27: 1007–1013. [PubMed: 19171716]
3. Ladenstein R, Potschger 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 2017; 18: 500–514. [PubMed: 28259608]

4. Pinto NR, Applebaum MA, Volchenboum SL et al. Advances in Risk Classification and Treatment Strategies for Neuroblastoma. J Clin Oncol 2015; 33: 3008–3017. [PubMed: 26304901]
5. 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 2004; 39: 931–936. [PubMed: 15185228]
6. Halperin EC. Long-term results of therapy for stage C neuroblastoma. J Surg Oncol 1996; 63: 172–178. [PubMed: 8944061]
7. Matthay KK, Atkinson JB, Stram DO et al. Patterns of relapse after autologous purged bone marrow transplantation for neuroblastoma: a Childrens Cancer Group pilot study. J Clin Oncol 1993; 11: 2226–2233. [PubMed: 8229138]
8. Mullassery D, Farrelly P, Losty PD. Does aggressive surgical resection improve survival in advanced stage 3 and 4 neuroblastoma? A systematic review and meta-analysis. Pediatr Hematol Oncol 2014; 31: 703–716. [PubMed: 25247398]
9. Wolden SL, Gollamudi SV, Kushner BH et al. Local control with multimodality therapy for stage 4 neuroblastoma. Int J Radiat Oncol Biol Phys 2000; 46: 969–974. [PubMed: 10705019]
10. 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 2013; 14: 999–1008. [PubMed: 23890779]
11. Kushner BH, Wolden S, LaQuaglia MP et al. Hyperfractionated low-dose radiotherapy for high-risk neuroblastoma after intensive chemotherapy and surgery. J Clin Oncol 2001; 19: 2821–2828. [PubMed: 11387353]
12. Bradfield SM, Douglas JG, Hawkins DS et al. Fractionated low-dose radiotherapy after myeloablative stem cell transplantation for local control in patients with high-risk neuroblastoma. Cancer 2004; 100: 1268–1275. [PubMed: 15022296]
13. Simon T, Hero B, Bongartz R et al. Intensified external-beam radiation therapy improves the outcome of stage 4 neuroblastoma in children > 1 year with residual local disease. Strahlenther Onkol 2006; 182: 389–394. [PubMed: 16826357]
14. Yahalom J, Mauch P. The involved field is back: issues in delineating the radiation field in Hodgkin's disease. Ann Oncol 2002; 13 Suppl 1: 79–83. [PubMed: 12078908]
15. Brodeur GM, Pritchard J, Berthold F et al. Revisions of the international criteria for neuroblastoma diagnosis, staging, and response to treatment. J Clin Oncol 1993; 11: 1466–1477. [PubMed: 8336186]
16. Bagatell R, Grupp SA. Refining megatherapy, improving outcome in neuroblastoma. Lancet Oncol 2017; 18: 423–424. [PubMed: 28259607]
17. Ducassou A, Gambart M, Munzer C et al. Long-term side effects of radiotherapy for pediatric localized neuroblastoma : results from clinical trials NB90 and NB94. Strahlenther Onkol 2015; 191: 604–612. [PubMed: 25896312]
18. Yalcin B, Kremer LC, Caron HN, van Dalen EC. High-dose chemotherapy and autologous haematopoietic stem cell rescue for children with high-risk neuroblastoma. Cochrane Database Syst Rev 2013; CD006301. [PubMed: 23970444]
19. Panandiker AS, Winchell A, Loeffler R et al. 4DMRI Provides More Accurate Renal Motion Estimation in IMRT in Young Children. Pract Radiat Oncol 2013; 3: S1.
20. Hattangadi JA, Rombi B, Yock TI et al. Proton radiotherapy for high-risk pediatric neuroblastoma: early outcomes and dose comparison. Int J Radiat Oncol Biol Phys 2012; 83: 1015–1022. [PubMed: 22138463]
21. Park JR, Scott JR, Stewart CF et al. Pilot induction regimen incorporating pharmacokinetically guided topotecan for treatment of newly diagnosed high-risk neuroblastoma: a Children's Oncology Group study. J Clin Oncol 2011; 29: 4351–4357. [PubMed: 22010014]

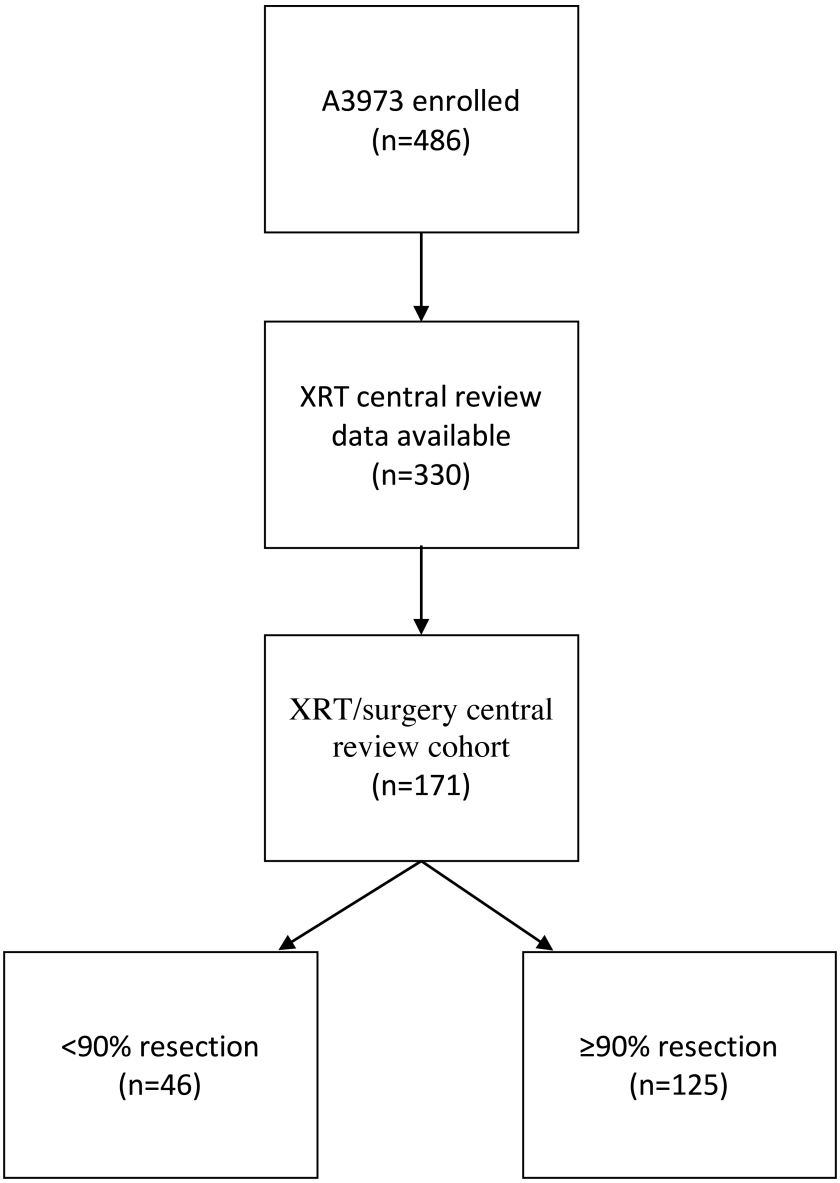

Figure 1.
CONSORT diagram depicting the analytic patient cohorts.

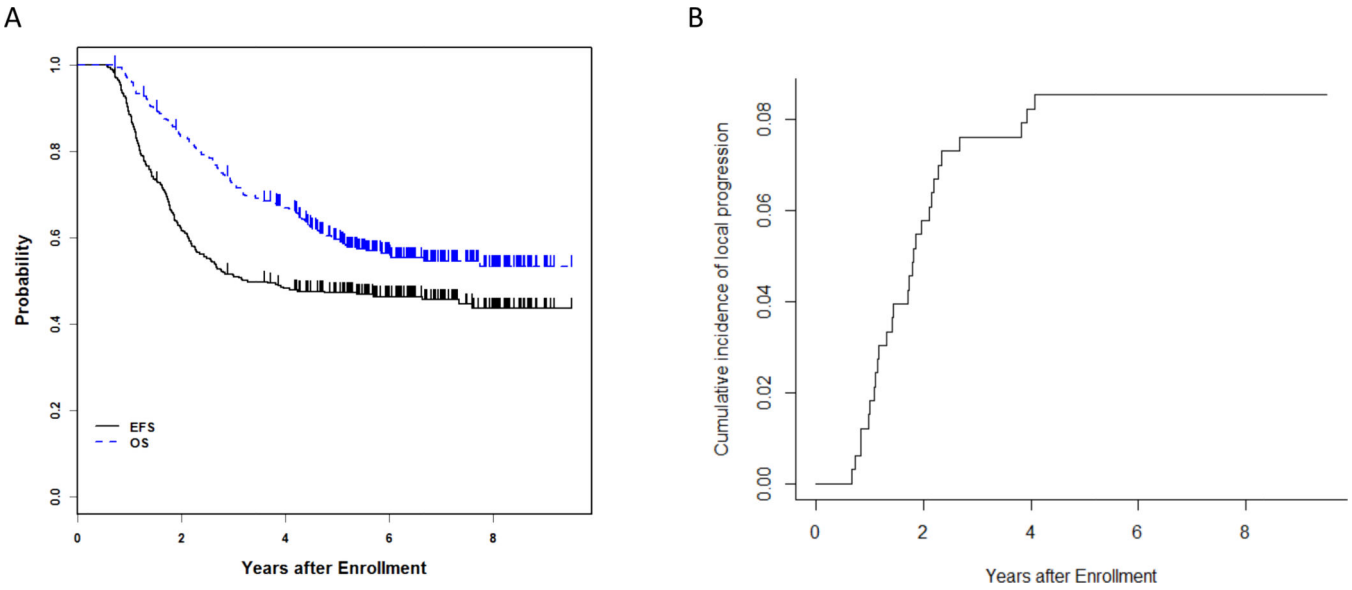

Figure 2.

Outcome for 330 patients receiving centrally reviewed radiotherapy on COG A3973. (A) Event-free survival and overall survival; (B) Cumulative incidence of local progression

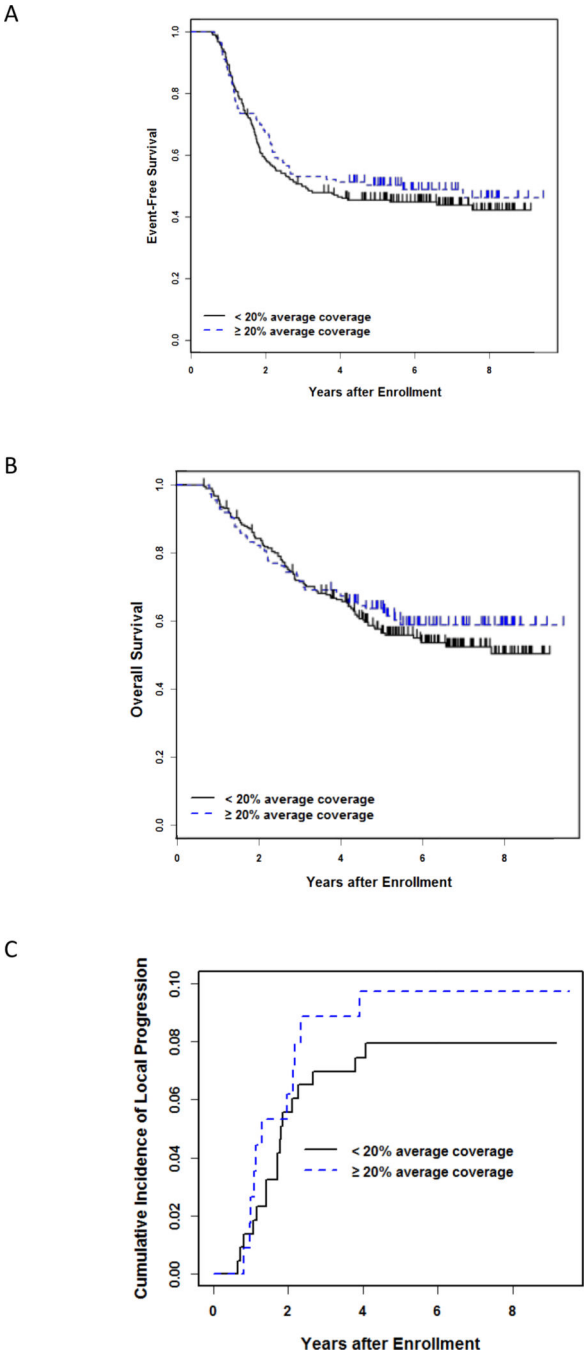

Figure 3.

Outcome by average percent lymph node radiation coverage: <20% (n=217) versus ≥20% (n=113), where 20% coverage is the third-quartile. (A) Event-free survival (p=0.5); (B) Overall survival (p=0.4); and, (C) Cumulative incidence of local progression (p=0.6)

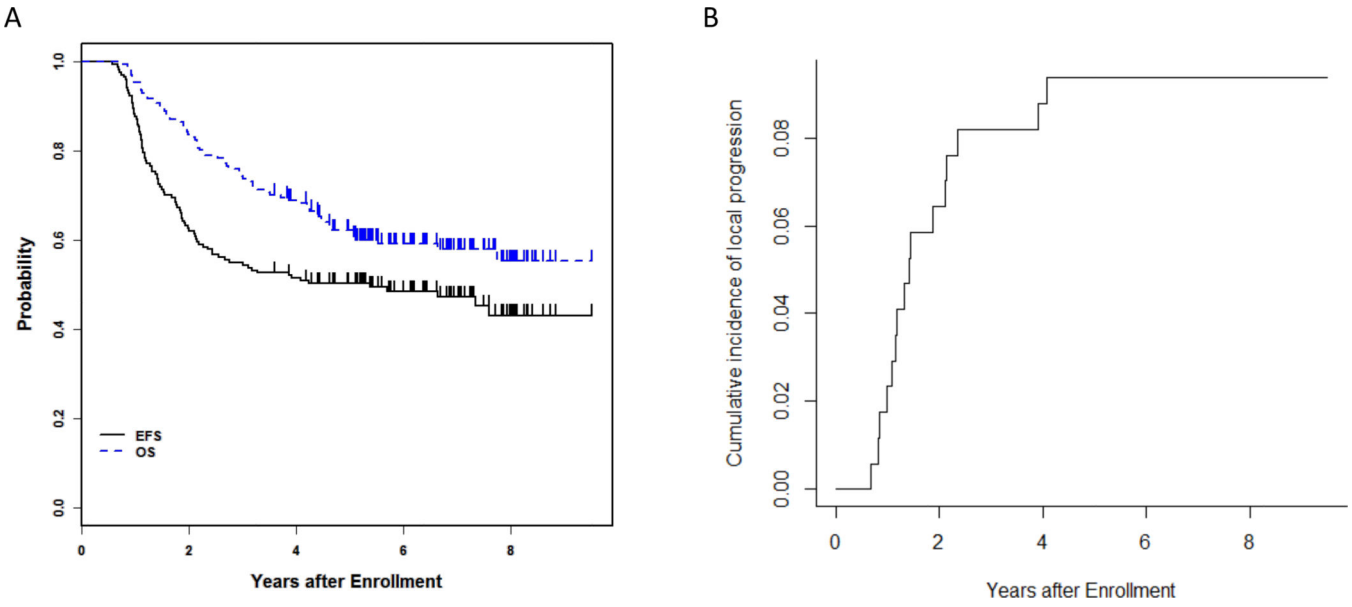

Figure 4.

Outcome for 171 patients in the radiation/surgery central review cohort on COG A3973. (A) Event-free survival and overall survival; (B) Cumulative incidence of local progression.

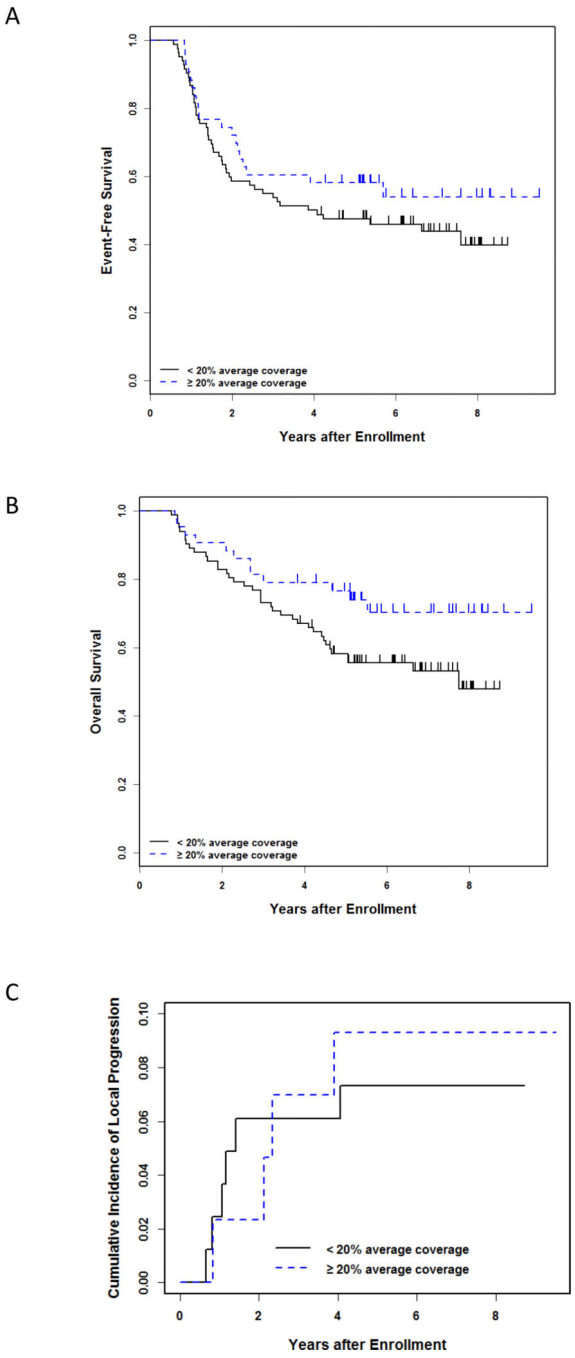

Figure 5.

Outcome for 125 patients in the radiation/surgery central review cohort who had ≥90% extent of primary tumor resection, by average percent lymph node radiation coverage: <20% (n=82) versus ≥20% (n=43). (A) Event-free survival (p=0.2); (B) Overall survival (p=0.06); (C) Cumulative incidence of local progression (p=0.7)

TABLE 1.

Patient characteristics (N=330)

Characteristic	N (%)	<20% average LNC N (%) (n=217)	≥20% average LNC N (%) (n=113)	Chi-squared p-value
Age at diagnosis				
<18 months	45 (14%)	29 (13%)	16 (14%)	0.8
≥18 months	285 (86%)	188 (87%)	97 (86%)	
INSS stage				
2, 3	49 (15%)	29 (13%)	20 (18%)	0.3 *
4	277 (84%)	184 (85%)	93 (82%)	
4S	4 (1%)	4 (2%)		
MYCN status				
Not amplified	164 (58%)	103 (56%)	61 (62%)	0.4
Amplified	118 (42%)	80 (44%)	38 (38%)	
Unknown	48	34	14	
Histology				
Favorable	9 (4%)	7 (4%)	2 (2%)	0.5 *
Unfavorable	246 (96%)	157 (96%)	89 (98%)	
Unknown	75	53	22	
Ploidy				
Hyperdiploid	135 (48%)	86 (48%)	49 (49%)	0.9
Diploid	145 (52%)	93 (52%)	52 (51%)	
Unknown	50	38	12	
End induction response				
CR or PR	307 (94%)	197 (60%)	110 (34%)	0.02 *
<PR	19 (6%)	17 (5%)	2 (1%)	
unknown	4	3	1	
Rec'd immunotherapy post-transplant on a COG study				0.2
Yes	75 (23%)	54 (16%)	21 (6%)	
No	255 (77%)	163 (50%)	92 (28%)	

* Fisher's exact test p-value