Clinicopathologic Features and Long-term Outcomes of NUT Midline Carcinoma


Abstract

Purpose: NUT midline carcinoma (NMC) is a poorly differentiated squamous cancer characterized by rearrangement of the NUT gene. Research advances have provided opportunities for targeted therapy in NMC, yet the clinical features of this rare disease have not been systematically characterized. We report on a large population of such patients to identify the disease characteristics and treatments, correlate them with outcome, and to consider clinical recommendations.

Experimental Design: A clinical database was established using retrospective demographic and outcomes data available on all known cases of NMC. Questionnaires were completed by treating physicians. Pathologic, demographic, and clinical variables were assessed for 63 patients, the largest cohort of patients with NMC studied to date. Outcome data from 54 patients were available for survival analyses.

Results: The diagnosis of NMC has increased annually since 2007. Since 2009, there has been an observed increase in the age at diagnosis (P < 0.05). Geographic distribution of patients with NMC has been concentrated in the United States (n = 41, 65%). The median overall survival for patients with NMC was 6.7 months. The 2-year progression-free survival (PFS) was 9% with a 95% confidence interval (CI) of 1% to 17% [1-year PFS 15% (5–24%) and 2-year overall survival (OS) was 19% with a 95% CI of 7%–31% (1-year OS: 30% [27–34%]). Multivariate analysis suggested that extent of surgical resection and initial radiotherapy were independent predictors of PFS and OS. Notably, no chemotherapeutic regimen was associated with improved outcome.

Conclusions: NMC portends a poor prognosis among all squamous cell neoplasms and seems to be frequently unrecognized. The finding that conventional chemotherapy has been inadequate indicates a pressing need for the development of targeted therapeutics. Intensive local therapies such as gross total resection and radiotherapy might be associated with enhanced survival. Clin Cancer Res; 18(20); 5773–9. ©2012 AACR.

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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doi: 10.1158/1078-0432.CCR-12-1153

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Introduction

NUT midline carcinoma (NMC) is an aggressive, genetically defined subset of human squamous cell carcinoma characterized by chromosomal rearrangement of the NUT gene (also known as Chr15orf55; ref. 1). Somatic rearrangement of the NUT gene in cancer was identified in 2003 (2), in the context of the characteristic (15;19) translocation that positions NUT in-frame with BRD4, a ubiquitously expressed transcriptional coactivator. A subset of NMCs lack BRD4 rearrangement and are termed NUT variants. Many of these tumors reveal NUT rearrangement to a gene family member, BRD3, whereas others possess, as yet, unresolved molecular biology (3). Histologically, NMC displays variable degrees of squamous differentiation with a predominance of the poorly differentiated component.

Although initially described in children and adolescents, NMC has subsequently also been observed in adults (4). As the cytogenetic and molecular evaluation of carcinomas in...
translated relevance

NUT midline carcinoma is caused by a recurrent gene fusion event resulting in cellular epigenetic deregulation. We created an international registry for NUT midline carcinoma patients and describe the clinicopathologic features and long-term outcomes of this disease. The rate of diagnosis continues to increase, especially in adults, suggesting this carcinoma remains underdiagnosed. We show the dismal response rate, progression-free survival, and overall survival characteristics of this disease. Although intensive local control seems associated with modest extension of survival, no specific chemotherapy regimen is clearly associated with superior outcome. Given the specific molecular derangement caused by BRD-NUT gene fusion and poor outcomes to conventional therapies, we anticipate this disease will make an excellent candidate for rational investigation of targeted inhibitors. These results establish a robust baseline against which future therapeutic interventions may be compared.

Adults is often limited, the actual incidence and clinical manifestations of NMC remain unclear. Isolated case reports and small case series reveal several common clinical features (2–23). NMC typically arises within midline head and neck structures or in the thorax and shows an aggressive behavior with early locoregional invasion and distant metastases. Treatment approaches have been heterogeneous. Although a single case report showed excellent outcome (15), other reported outcomes have been poor.

Since its recognition as a genetically defined cancer (2, 18), many cases of NMC have come to our attention because of our unique ability to conduct testing for the characteristic gene rearrangements and aberrant antigen expression. Over the past decade, we have served as the primary diagnostic center for NMC for many pathologists in North America and Europe. This concentration of cases provided a unique opportunity to develop an international registry, established in 2010, in which retrospective clinical and pathologic data served as the foundation for prospective data capture of clinical and therapeutic interventions, as well as analysis of outcomes. Here, we investigate the clinical features of 63 cases of NMC of which we are aware, either through histologic review at our institution (n = 59) or literature review (n = 4). We compared progression-free and overall survival on 54 evaluable patients with respect to demographic, molecular, and clinical features, as well as treatment variables including extent of surgical resection, provision of radiotherapy, and selected chemotherapeutic agents.

Materials and Methods

Patients

From 1990 to 2010, we learned of 63 patients with NMC who were defined as those with NUT rearrangement shown by FISH or reverse transcriptase (RT)-PCR, aberrant NUT expression shown by immunohistochemistry, or characteristic t(15;19) in the setting of carcinoma. Fifty-nine of them came to our attention in the context of rendering the molecular and/or histologic diagnosis. The other 4 cases were found by literature review (9, 11, 19). We have previously described 35 of these cases, albeit with limited annotation of clinical characteristics and outcomes (2, 4, 6, 12, 13, 15, 17, 18, 22, 24). In this study, we collected previously unpublished clinical data for 28 of these 35 cases and updated outcome data for all 35 (Supplementary Table S1). In addition, we describe 24 previously unpublished cases. All cases known to us and diagnosed before August 2010 were included. Nineteen of the 63 cases were diagnosed by retrospective review of pathology material and 44 were diagnosed at the time of initial presentation.

For 56 cases, a questionnaire was sent to treating physicians inquiring about demographic, clinical, treatment, and outcome variables. Outcome data were submitted for 54 patients. Approval for the International NMC Registry (www.nmcregistry.org), including the retrospective and prospective analysis of NMC patient data, was obtained from the Institutional Review Board of the Dana-Farber Cancer Institute (Boston, MA). Review of retrospective clinical data was approved with a waiver of patient consent.

Patient data were collected and analyzed in aggregate; some outcome data were analyzed in 2 groups defined by age (age <18 years vs. age ≥18 years). Pathology reports and actual histology were reviewed when available. For the purposes of this study, cases were classified into 3 histopathologic categories: carcinoma with squamous differentiation, carcinoma without squamous differentiation, and other histology. Clinical staging data (site of primary tumor, lymph node involvement, and location of metastasis), as well as the response to therapeutic interventions, were provided by the treating physician. Initial therapy was defined as treatment administered from initial diagnosis until first relapse or progression. Surgical extent was classified as gross total resection (no residual disease or microscopic residual disease) or less than gross total resection. Chemotherapy was categorized into regimens containing either cisplatin or carboplatin, or regimens containing anthracyclines and nonplatinum alkylating agents. Many patients received combination therapy, thus there exists some overlap between these groups. Therapy initiated following relapse or progression was not analyzed. For patients who were alive at the time of analysis, date of last contact was no later than March 2011, and no earlier than June 2010.

For progression-free survival (PFS), time-to-event was measured as the time from initial diagnosis of cancer at the treating hospital until the time of first disease relapse, progression or death, or until last contact if none of these events occurred. For overall survival (OS), time was measured from diagnosis until the time of death or until last contact. Clinical responses to initial therapies were classified as complete or partial responses, stable disease, or...
progressive disease according to the clinical judgment of the treating physician.

**Statistical analysis**

Kaplan–Meier plots and log-rank tests were carried out to assess factors associated with PFS or OS. One- and 2-year PFS and OS point estimates are presented with a 95% confidence interval (CI). Two-sided Fisher’s exact tests were carried out to assess factors associated with the presence of each NUT translocation. For these analyses, there was no correction for multiple testing. A Cox proportional hazards regression model was carried out to identify variables independently predictive of PFS or OS. Only variables that were statistically significant in the log-rank test were tested in the Cox model. For all analyses, $P < 0.05$ were considered statistically significant. For illustrative purposes, all graphical representations of data have been truncated at 3 years.

**Results**

**Demographic features**

Geographic and demographic features are summarized in Tables 1 and 2, respectively. Forty-one of 63 cases presented in the United States (Table 1). Table 2 includes the 54 cases for which outcome data were available. Of the 44 cases of NMC diagnosed at the time of initial presentation (“real-time,” as opposed to at the time of relapse or posthumously), 59% were recognized since 2006 (Fig. 1). Males and females were equally affected, and median age was 16 years (range 0.1–78 years; Table 2). As awareness of the disease has grown, there has been an apparent increase in the number of cases of NMC. The majority of tumors arose in the thorax ($n = 35, 56\%$), or head and neck ($n = 24, 21\%$), and presented with either lymph node involvement or distant metastases ($n = 32, 51\%$; Table 2).

**Outcomes**

Outcome data were available for 54 of 63 cases. The overall 1- and 2-year PFS was 15% (95% CI, 5–24) and 9% (95% CI, 1–17), respectively; and the 1- and 2-year OS 30% (95% CI, 27–34) and 19% (95% CI, 7–31), respectively ($n = 54$; Table 2). With a 31.8-month median follow-up time for living patients, the median OS was 6.7 months (range 0.7 months–19+ years; Fig. 2). As awareness of the disease has grown, there has been an apparent increase in the number of cases of NMC. The majority of tumors arose in the thorax ($n = 35, 56\%$), or head and neck ($n = 24, 21\%$), and presented with either lymph node involvement or distant metastases ($n = 32, 51\%$; Table 2).

**Table 1. Geographical distribution of NMC cases**

<table>
<thead>
<tr>
<th>Location</th>
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<tbody>
<tr>
<td>United States</td>
<td>41</td>
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<tr>
<td>Massachusetts</td>
<td>6</td>
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<tr>
<td>Virginia</td>
<td>5</td>
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<tr>
<td>Minnesota</td>
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<td>California</td>
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<td>New York</td>
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<td>Connecticut</td>
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<td>Georgia</td>
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<td>Maryland</td>
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<td>Pennsylvania</td>
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<td>Washington</td>
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<td>Florida</td>
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<td>Idaho</td>
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<td>Illinois</td>
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<td>Kentucky</td>
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<td>Maine</td>
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<td>Michigan</td>
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<td>New Mexico</td>
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<tr>
<td>Ohio</td>
<td>1</td>
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<tr>
<td>Italy</td>
<td>5</td>
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<tr>
<td>Australia</td>
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<tr>
<td>Sweden</td>
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<tr>
<td>Greece</td>
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<tr>
<td>Netherlands</td>
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<td>Switzerland</td>
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Abbreviation: NMC, NUT midline carcinoma.

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**Impact of therapeutic interventions**

PFS and OS were statistically significantly higher who received early administration of radiotherapy (Table 2, Fig. 3A). The total radiotherapy dose was evaluable for 18 of 26 patients. Seventeen received doses ranging from 30.0 to 66.6 Gy (median = 52.2 Gy), and a single patient received only 5.5 Gy. There was no observed difference in PFS or OS.
between the lower radiation dose group (dose ≤ 52.2 Gy) and the higher radiation dose group (dose > 52.2 Gy; P = 0.8 and 0.9, respectively). PFS and OS were statistically significantly higher with gross total resection compared with those who had less than gross total resection or no surgical resection (Table 2, Fig. 3B). Of the 5 cases with gross total resection, 2 showed microscopic residual disease and 3 had no residual disease. To identify factors independently prognostic of PFS and OS, extent of surgical resection, initial radiotherapy, tumor location (carried out for PFS only), and presence of metastases were tested in the Cox model. The extent of surgical resection and initial radiotherapy were independently predictive of PFS and OS. Patients who received less than a gross total surgical resection or no surgical resection had a 5-fold greater risk of progression (P = 0.03) and 8-fold greater risk of death (P = 0.05) compared with patients who underwent gross total surgical resection. Patients who did not receive initial radiotherapy had a 2.8 times greater risk of progression (P = 0.002) and 2.2 times greater risk of death (P = 0.01) compared with patients who received initial radiotherapy (Table 3).

The clinical response to combined initial therapies (including chemotherapy, radiotherapy, and surgery) could be evaluated in 51 patients: 8 had a complete response and 18 a partial response. Of the 8 CRs, 4 progressed, and 2 ultimately died. Median time to progression was 9.3 months with a range of 5.0 to 16.3 months. At last contact, between the lower radiation dose group (dose ≤ 52.2 Gy) and the higher radiation dose group (dose > 52.2 Gy; P = 0.8 and 0.9, respectively). PFS and OS were statistically significantly higher with gross total resection compared with those who had less than gross total resection or no surgical resection (Table 2, Fig. 3B). Of the 5 cases with gross total resection, 2 showed microscopic residual disease and 3 had no residual disease. To identify factors independently prognostic of PFS and OS, extent of surgical resection, initial radiotherapy, tumor location (carried out for PFS only), and presence of metastases were tested in the Cox model. The extent of surgical resection and initial radiotherapy were independently predictive of PFS and OS. Patients who received less than a gross total surgical resection or no surgical resection had a 5-fold greater risk of progression (P = 0.03) and 8-fold greater risk of death (P = 0.05) compared with patients who underwent gross total surgical resection. Patients who did not receive initial radiotherapy had a 2.8 times greater risk of progression (P = 0.002) and 2.2 times greater risk of death (P = 0.01) compared with patients who received initial radiotherapy (Table 3).

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the other 4 had not progressed. The follow-up times (from diagnosis) for these 4 patients were 2.6, 2.9, 3.2, and 19 years. Only those patients treated with initial surgical resection or radiation, with or without chemotherapy, had a complete response. The remaining 25 patients had stable or progressive disease. Complete response was positively associated with initial radiotherapy ($P = 0.002$), age less than 18 years ($P = 0.04$), and absence of metastases ($P = 0.04$). Clinical response to therapy was not significantly associated with NUT translocation subtype, tumor histology, sex, tumor location, or lymph node involvement. Cause of death (determined for 46 patients) was noted as tumor progression ($n = 44$), tumor lysis syndrome ($n = 1$), and septicemia ($n = 1$). In this analysis, there was no evidence that chemotherapy improved outcomes among the 53 patients who received it (Table 2).

**Discussion**

NMC is a genetically defined subtype of squamous carcinoma, in particular of the mediastinum, head, and neck. In an effort to better characterize the clinical outcomes of patients with NMC, we carried out a retrospective analysis of outcomes in all known cases. Until recently, testing for NUT rearrangement relied on a highly specialized FISH or RT-PCR assay, or cytogenetic analysis, which was unavailable in most laboratories. Since the description of NMC as an entity, we have served as the major diagnostic referral center for NMC. For this reason, this retrospective collection of all cases sent to us for review, as well as all published cases, represents the most comprehensive collection ever reported, and attempts to minimize selection bias. Despite inclusion of all cases known to us, the sample size remains small, and the results should be interpreted with caution. We will conduct validation analysis of all significant findings in a prospective, inclusive cohort.

Although we found both the incidence of NMC diagnosis and age at diagnosis seemed to be rising, we recognize that this might be a reflection of reporting bias of this still rare and likely underrecognized disease. For example, we noted a statistically significant difference in age between patients diagnosed between 2007 and 2008 [median age: 14 years (range = 0.1–40 years) and those diagnosed between 2009 and 2010 (median age: 29 years; range = 2–62 years; $P = 0.015$)]. In 2010, the number of adult cases of NMC ($n = 7$) outnumbered pediatric cases ($n = 1$). Our findings suggest that NMC remains underrecognized, in particular among adult patients. Indeed, it is uncommon for tissue derived from adult patients to be assessed for cytogenetic abnormalities that historically established the diagnosis of NMC. Recently, a simple immunohistochemical stain for the NUT gene product was developed, using a commercially available clinical immunoglobulin, which in the context of evaluating patient-derived tumor specimens is highly sensitive and specific for NMC (17). With increased awareness...
have a 6.7-month median survival and a greater than 80% poor prognosis of patients diagnosed with NMC, who hypothesis for experimental evaluation. BRD4–NUT ular subtypes with unique prognostic features. We note that identification of the fusion partner of NUT longests survivors in our series had ever studied. Nonetheless, it was intriguing that 5 of 7 the fact that this is the largest cohort of patients with NMC proven to be 100% specific and highly sensitive (87%) for the diagnosis of NMC (17). Characterization of the fusion gene (BRD4–NUT and BRD3–NUT) is not required for the diagnosis, but is recommended, either by FISH, cytogenetics, or RT-PCR.

In contrast to a previous case series that suggested an improved outcome for NUT-variant NMC (18), our more comprehensive study failed to identify a significant association between translocation type (BRD4–NUT, BRD3–NUT, or NUT-variant) and outcome. This might be due to a lack of sufficient power for detecting small differences, inspite of the fact that this is the largest cohort of patients with NMC ever studied. Nonetheless, it was intriguing that 5 of 7 longest survivors in our series had BRD3–NUT (n = 1) or NUT-variant (n = 4) fusions. It is possible that improved identification of the fusion partner of NUT-variant carcinomas and longer follow-up might identify specific molecular subtypes with unique prognostic features. We note that the vast majority of head and neck NMC (88%) harbored BRD4–NUT translocations. Given that the cell of origin of NMC remains unknown, this association establishes a hypothesis for experimental evaluation.

The most striking finding of this study is the extremely poor prognosis of patients diagnosed with NMC, who have a 6.7-month median survival and a greater than 80% likelihood of death within the first year after diagnosis for adult patients. Heterogeneous systemic therapies have been used to treat patients with NMC, including intensive chemotherapy regimens commonly used in the treatment of germ cell tumors, squamous cell carcinoma of the head and neck, non–small cell lung carcinoma, and sarcoma. Many of those regimens have used platinum agents, anthracyclines, and nonplatinum alkylating agents alone or in combination. Because of the fact that most patients received a combination of therapies, we were unable to conduct an analysis that identified specific chemotherapeutic agents with improved outcomes. Many patients with NMC were observed to respond initially to combined modality treatment but the overall outcomes for these patients remained very poor. There remains only one known long-term survivor of NMC, who was treated with radiotherapy and chemotherapy (15). This solitary successful case possessed unique features, including histology without features of carcinoma and primary location within bone. Our overall findings suggest that intensive local control was associated with modest extension of survival.

NMC exemplifies the paradigmatic shift in clinical oncology brought by the molecular characterization of cancer, as a disease unified not anatomically but rather by a common genetic pathophysiology, which reprograms the tumor epigenome (24) and confers catastrophic clinical consequences. Recent biologic advances in the laboratory study of NMC show that bromodomain-containing NUT fusion proteins result in aberrant histone acetylation (24) and blockade of differentiation (3). These key findings have established hyperacetylation therapy, using histone deacetylase inhibitors, as a mechanism-based investigational approach (24). Recently, our group developed first-in-class, direct-acting inhibitors of the BRD3 and BRD4 bromodomains, as targeted therapy for NMC (25). A prototype bromodomain inhibitor, JQ1, exhibits potent differentiating activity in vitro, and confers prolonged survival in patient-derived and primary xenograft models of NMC. The clinical translation of this research requires robust, historical outcome data and a coordinated, flexible network of

![Table 3. Multivariable analysis of factors independently prognostic of PFS and OS](image)

<table>
<thead>
<tr>
<th>Factors with increased risk of progression</th>
<th>HR (95% CI)</th>
<th>P value</th>
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<tbody>
<tr>
<td>Incomplete or no surgical resection</td>
<td>5.00 (1.12–22.2)</td>
<td>0.03</td>
</tr>
<tr>
<td>No initial radiotherapy</td>
<td>2.82 (1.48–5.29)</td>
<td>0.002</td>
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<tr>
<th>Factors with increased risk of death</th>
<th>HR (95% CI)</th>
<th>P value</th>
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<tbody>
<tr>
<td>Incomplete or no surgical resection</td>
<td>7.94 (1.03–62.5)</td>
<td>0.05</td>
</tr>
<tr>
<td>No initial radiotherapy</td>
<td>2.20 (1.18–4.09)</td>
<td>0.01</td>
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</table>

| a Tested in the model and found to be not statistically significant were: tumor location [HR = 1.13; 95% CI, 0.72–1.78; P = 0.6] and metastases [HR = 1.47; 95% CI, 0.80–2.69; P = 0.2]. |
| b Tested in the model and found to be not statistically significant was tumor location [HR = 1.10; 95% CI, 0.58–2.09; P = 0.8]. |
patients and providers assembled around the study and eradication of this malignancy. This is a challenge shared with many rare malignancies: it is only through the development of integrated, multinational, and international initiatives that advances in the understanding and treatment of these cancers can occur. We hope that the establishment of the International NMC Registry (www.nmcregistry.org) will serve as the first step toward this goal.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors' Contributions
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): D. Bauer, C. Mitchell, E. Stelow, S. Luer, S. Muthammer, A. Evans, L. Sholl, I. Rosal, R.-G. Carlos, S. E. Sallan, J. Bradner, C. A. French
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Writing, review, and/or revision of the manuscript: D. Bauer, C. Mitchell, E. Stelow, S. Luer, S. Muthammer, A. Evans, E. Giraldi, R.-G. Carlos, W. London, S. E. Sallan, J. Bradner, C. A. French
Administrative, technical, or material support (i.e., reporting and organizing data, constructing databases): C. Mitchell, K. Strait, C. Lathan, S. Luer, R. Oakley, W. London, S. E. Sallan, J. Bradner, C. A. French
Study supervision: D. Bauer, C. Mitchell, R.-G. Carlos, J. Bradner, C. A. French

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): D. Bauer, K. Strait, E. Stelow, W. London, S. E. Sallan, J. Bradner, C. A. French
Grant Support
This work was supported by the Adolescent and Young Adult Cup Fund (to J. E. Bradner and C. A. French), the Smith Family Foundation (to J. E. Bradner) and the NIH grants 3R01CA124581-03S1 (to C. S. Lathan), R01CA124633, and R01CA124633-04S1 (to C. A. French). The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received April 9, 2012; revised July 20, 2012; accepted July 31, 2012; published OnlineFirst August 15, 2012.

References
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