1042 Long-Term Update of a Prospective Randomized Trial of Combined-Modality Therapy Versus Chemotherapy in Advanced Hodgkin's Disease

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Purpose/Objective: The role of consolidation radiotherapy (RT) in the treatment of advanced Hodgkin's disease (HD) is controversial. Several randomized trials have addressed this issue with contradictory results. The follow-up in these trials has generally been short and questions have often been raised concerning protocol violations, specifically adherence to radiotherapy guidelines. This paper presents long-term results of a prospective randomized trial of consolidation radiotherapy in advanced HD carried out at Duke University Medical Center.

Materials/Methods: Between 1982 and 1986, 30 patients with advanced HD (stages IIB–IV) were enrolled in a Southeastern Cancer Study Group (SEG 81-328) prospective trial of chemotherapy (CT) alone vs. combined-modality therapy (CMT) at Duke University Medical Center. This was a multi-institutional trial, but the dissolution of the SEG led to the loss of data from other institutions. All patients received induction chemotherapy consisting of six to ten cycles of BCNU, cyclophosphamide, vinblastine, procarbazine, and prednisone (BCVPP). Complete responders and good partial responders were then randomized to either involved field consolidation radiotherapy (n = 15) or no further treatment (n = 15). RT doses ranged from 1800 to 3100 cGy (median 2300) and were delivered to sites of HD present prior to the onset of chemotherapy without regard to bulk of disease. Overall survival (OS), failure-free survival (FFS), and cause-specific survival (CSS), determined by the Kaplan-Meier method, were compared by the log rank test. P values ≤ 0.05 constituted statistical significance.

Results: Despite small numbers of patients, the groups were balanced with respect to stage. Median follow-up of surviving patients is 17 years. Ten-year survivals (OS, FFS, CSS) are shown in Table 1 for CT and CMT patients. By each measure, outcome was improved in the CMT group. Causes of death for the two groups are shown in Table 2. Overall, there were 13 deaths, 7 of which were due to HD, 4 to second cancers (3 leukemias and 1 mycosis fungoides), and 2 to unrelated causes (1 myocardial infarction in the CT group and 1 cerebral vascular accident in the CMT group). Eleven patients have relapsed, 8 in the CT group and 3 in the CMT group. Four of these 11 were successfully salvaged with additional treatment and remain free of HD, 3 in the CT and 1 in the CMT group. For the 8 patients relapsing in the CT group, 3 failed at sites of original disease, 2 in areas of original disease as well as new sites and 3 in previously uninvolved sites alone. For the CMT group, 1 patient failed in the radiation field and 2 failed at distant sites.

Conclusions: CMT significantly improved FFS and OS in this carefully controlled phase III trial employing low dose RT, albeit the numbers are small and the CT regimen did not include anthracyclines. There was a non-significant improvement in CSS. There was no suggestion of increased complications in the CMT patients compared with the CT group. Specifically, 3 second malignancies were observed in the CT group and only 1 in the CMT group. Implications for future trials will be discussed.

Table 1. **10-Year Survival (%)**

	OS (p = 0.05)	FFS (p = 0.04)	CSS (p = 0.12)
CT	46	39	59
CMT	69	79	83

Table 2. **Causes of Death**

	Hodgkin's Disease	2nd Malignancy	Other	Total
CT	5	3	1	9
CMT	2	1	1	4

1043 Primary Spinal Epidural Lymphoma: Outcome and Prognostic Factors in Patients Treated with Radiotherapy: A Multicenter Rare Cancer Network (RCN) Study

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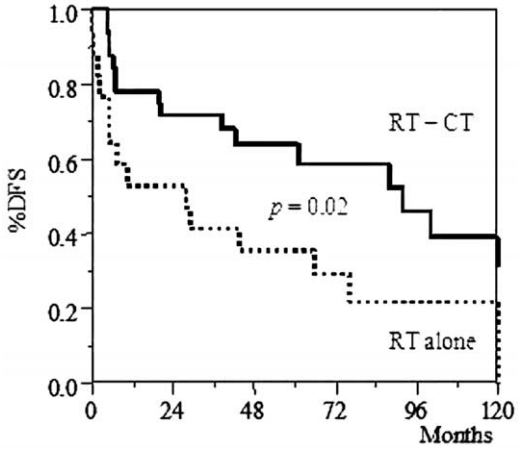
Purpose/Objective: Primary spinal epidural lymphoma (PSEL) represents less than 10% of epidural tumors, and less than 1% of all non-Hodgkin's lymphomas (NHL). The goal of this study was to assess the clinical profile treatment, treatment outcome, and prognostic factors of this rare entity.

Materials/Methods: Between 1982 and 2000, 49 consecutive patients with PSEL were treated in 8 institutions of the RCN. The most common symptoms were back pain (82%), motor weakness (94%), sensory deficits (67%), and sphincter dysfunction (20%). Diagnostic work-up included a spinal CT scan (77% of patients) and/or MRI (51%), whole-body CT-scan (96%), bone marrow aspiration/biopsy (88%), and all patients had biopsy-proven confirmation of the NHL. According to the Working Formulation classification, 12 patients had low-grade, 26 intermediate, and 11 high-grade NHL. Forty-five patients had an Ann-Arbor stage I and 5 had a stage II. Forty patients underwent decompressive laminectomy, all received radiotherapy (RT)

alone (n = 17) or combined with chemotherapy (CTX) (n = 32). Median RT dose was 35 Gy (range: 6–44). Median follow-up was 71 months (range: 22–165).

Results: Following therapy, neurological (motor) response to treatment was complete in 22% of patients, and partial in 67%. Follow-up examinations revealed that 7 (14%) patients progressed locally, and 21 (43%) had a systemic relapse. Those were mainly in lymph nodes (n = 9), bone marrow (n = 5), or CNS (n = 4). At last follow-up, 27 patients were alive (4 with disease), and 22 had died (17 with disease). The 5-year overall- (OS), lymphoma-specific- (LSS), disease-free survival (DFS), and local control (LC) were 68%, 71%, 50%, and 86%, respectively. In univariate analyses, favorable prognostic factors were upper lesions, age < 64, high grade, neurological response, negative CSF examination, and combined chemo-radiotherapy (Figure). Multivariate analysis showed that favorable neurological response, the type of surgery, RT dose, and combined treatment were significant. No major complication was reported.

Conclusions: Primary spinal epidural lymphoma has distinct clinical features and outcome, with a relatively good prognosis. After therapy, local control is excellent but systemic relapse occurs in about half of cases. Combined modality appears to be superior to RT alone.



1044 External Beam Radiation Therapy after ^{90}Y-Ibritumomab Tiuxetan Radioimmunotherapy for Relapsed or Refractory CD20+ Non-Hodgkin's Lymphoma

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Purpose/Objective: ^{90}Y-Ibritumomab tiuxetan (Zevalin®) has proven safety and efficacy in the treatment of relapsed and refractory B-cell NHL. A phase III trial randomizing patients to treatment with either Zevalin® radioimmunotherapy (RIT) or "cold" rituximab revealed clinically and statistically improved overall response rates and prolonged treatment-free intervals. Unfortunately, many patients will have persistent tumor or eventually relapse after RIT. In the aforementioned study, patients with bulky disease sites (≥ 5cm) had a lower overall response rate than the RIT-treated group as a whole. This observation suggests that the absorbed radiation dose delivered with standard dosages of Zevalin® may be inadequate to provide durable control of large tumors. The exact role of external beam radiation therapy (EBRT) for persistent or recurrent disease after RIT has not been defined. The purpose of this retrospective study was to assess the efficacy and toxicity of EBRT in this setting.

Materials/Methods: Records of 135 relapsed B-cell NHL patients treated with Zevalin® on clinical trials were reviewed to identify those patients who subsequently received EBRT. Radiation treatment records and blood counts were reviewed for evidence of acute or chronic radiation-induced toxicity and treatment responses. The NCI-International Working Group criteria were used to assess tumor responses within the irradiated fields. Toxicities were retrospectively graded using the Common Toxicity Criteria, version 2.0.

Results: Nineteen patients received EBRT to a total of 39 tumor sites following RIT. Records for 3 patients (3 tumor sites) were unavailable for analysis. Forty-four percent of recurrent tumors (16/36) were characterized as "bulky" (≥ 5cm). The median radiation dose delivered per treatment course was 28.5 Gy (range, 10–40), with median fraction size 2 Gy (range, 1–5 Gy). Median elapsed time between RIT and the start of EBRT was 8.2 months (range, 1–63). Responses were observed in 26 of 36 tumor sites (72%), including 12 sites with complete responses (33%), 7 with complete clinical responses (19%), and 7 with partial responses (19%). Eight percent of tumor sites (3/36) remained stable. Responses were not documented for 7 irradiated tumor sites in 2 terminally ill patients. For "bulky" tumor sites (n=16), the overall and complete response rates were 87% (14/16) and 25% (4/16), respectively. The incidences of gr. 1–2 and gr. 3–4 acute/subacute adverse events were 50% and 8% respectively (see Table). One patient with pre-existing renal insufficiency developed tumor lysis syndrome and resultant renal failure while under treatment. This adverse event was not felt to represent a direct nephrotoxic effect of the radiation. The remaining documented adverse events were transient, reversible, and corresponded to the anatomic regions irradiated.

Conclusions: EBRT after Zevalin® RIT appears to be safe and well-tolerated. The frequency and severity of adverse events observed in this extensively pre-treated cohort were not above what could reasonably be expected in previously untreated patients. Excellent response rates were achieved in these patients despite the prior administration of systemic radioimmunotherapy, even in patients with bulky tumors. Our results suggest that recurrence or relapse after Zevalin® RIT does not signify radioresistance.