Radiation Oncology Research in the Cancer and Leukemia Group B

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Abstract

Radiation oncology initiatives have been an integral component in the evolution of multidisciplinary research in the Cancer and Leukemia Group B. Although early studies in the Group primarily focused on chemotherapy for hematologic and pediatric malignancies, the Radiation Oncology Committee was established in 1972, reflecting the broadening scope of clinical investigation with an increased emphasis on solid tumor research. A major early contribution of the Radiation Oncology Committee was the recognition of the importance of formalized radiation quality review, which led to the development of the Quality Assurance Review Center. The committee has been instrumental in designing trials, in conjunction with our medical oncology and surgical oncology colleagues, to assess multimodality therapy. The results of many of these studies have had important implications for clinical practice. Recent efforts have explored our major research theme of treatment intensification via radiotherapy dose modulation and novel combinations of radiotherapy with sensitizing agents, with an emphasis on safely implementing advanced technologies in the cooperative group setting.

The Acute Leukemia Group B was formed in 1956 with the purpose of doing controlled clinical trials in the acute leukemias. During the 1960s, research expanded to include both pediatric and adult solid neoplasms. As the emphasis on multimodality solid tumor research increased during the 1970s, the Radiation Oncology Committee was formally established to reflect this mission. Accordingly, the name of the group was changed to the Cancer and Leukemia Group B (CALGB) in 1976, and the focus of the Group was subsequently limited to adult malignancies when the Pediatric Oncology Group was formed in the early 1980s from the pediatric divisions of both the Southwest Oncology Group and the CALGB. The primary charge of the Radiation Oncology Committee has been to work in concert with our medical oncology and surgical oncology partners to develop advances in multimodality cancer treatment. The major hypothesis guiding radiation research initiatives is that increasing the intensity of local therapy will enhance local tumor control and survival, particularly in an era of increasingly effective systemic therapy.

Several CALGB accomplishments have contributed to advancing radiation oncology research (see below). The CALGB Radiation Oncology Committee pioneered the development of a cooperative group radiation oncology quality assurance program. The quality assurance function has remained strong and facilitated early integration and assessment of advanced radiotherapy technologies in multimodality cooperative group trials. Phase III studies have addressed seminal questions, including the optimal timing of radiotherapy relative to chemotherapy in diseases where both modalities are indicated, whereas other randomized trials have tested whether radiotherapy administration is necessary in certain clinical situations where the role of radiotherapy had not previously been defined. Pilot studies exploring strategies to enhance treatment efficacy, through radiotherapy dose modulation or novel integration of radiotherapy with sensitizing agents, have yielded data supporting subsequent phase III initiatives.

Selected Highlights of Radiation Oncology Research in the CALGB

- Pioneered radiotherapy quality assurance in the cooperative group setting
- Designed the first cooperative group multi-institutional trial assessing extended field radiotherapy for Hodgkin’s disease
- Early identification of the potential neuropsychiatric consequences of cranial radiotherapy in children with ALL
- Strengthened concerns regarding the relationship between radiotherapy and late secondary solid malignancies in Hodgkin’s disease
- Assessed the timing of radiotherapy relative to chemotherapy in lung cancer and node-positive breast cancer
- Conducted multiple trials assessing high-dose radiotherapy (e.g., ≥70 Gy) in lung cancer
- Provided pilot data for novel radiotherapy/drug combinations in gastrointestinal malignancies that supported the development of phase III trials
- Developed the initial studies specifically targeted toward patients with early lung cancer and cardiopulmonary dysfunction
- Completed the first phase II cooperative group trial of conformal radiotherapy in lung cancer
Radiotherapy quality assurance

A major early contribution of the CALGB Radiation Oncology Committee was the development of a quality assurance program for radiotherapy trials. The Quality Assurance Review Center originated in the CALGB to help ensure appropriateness and uniformity of treatment throughout the cooperative group. This program included on-treatment review of patient specific radiotherapy data, and Quality Assurance Review Center has since expanded to serve the majority of cooperative groups in the United States. The effect of a formal interventional quality review process was immediately evident. Early after implementing the program in 1977, ~50% of all radiotherapy data were available for review and the protocol deviation rate was ~40%. Feedback to institutions and presentations of problems at Group meetings improved compliance with protocols, and by 1979, 90% of radiotherapy data were available with a <5% deviation rate (1). Several critical reviews of radiotherapy data have been instrumental to improving the quality of oncology practice. Early studies assessed pitfalls in the design of treatment fields for cranial radiotherapy in acute lymphoblastic leukemia (ALL) and showed that radiotherapy technique affected tumor control in limited-stage small cell lung cancer (LSCLC; refs. 2, 3). More recent quality assurance reviews identified considerations for treatment planning in breast cancer, LSCLC, and non–small cell lung cancer (NSCLC; refs. 4–6). The quality review process has been critical in implementing advances in both radiographic imaging and radiotherapy planning. For example, CALGB was the first cooperative group to complete a phase II group-wide study requiring three-dimensional conformal radiotherapy in NSCLC, and recent trials in esophageal and lung cancer have integrated functional imaging (e.g., 18-fluorodeoxy-D-glucose positron emission tomography) in the radiotherapy treatment planning process (7–9).

Early trials in pediatric and hematologic malignancies

Long-term evaluation of cranial radiotherapy in pediatric ALL. CALGB 7611 randomized children and adolescents ages <20 years with ALL who achieved complete remission to receive intermediate dose i.v. methotrexate (500 mg/m² × 3) or cranial irradiation to a dose of 2,400 cGy in 200 cGy fractions (10). Patients on both study arms also received intrathecal methotrexate. A mature report with 10-year follow-up published in 1997 included 525 evaluable children. Although the 12-year continuous complete remission rates were similar in both arms (40%), protection against hematologic relapse was superior for children randomized to intermediate dose methotrexate, whereas reduced central nervous system relapse was noted for children randomized to receive cranial radiotherapy. This study provided important insight into the potential neuropsychiatric ramifications of cranial radiotherapy in children. Patients who received cranial radiotherapy had significantly lower full-scale intelligence quotient scores and did more poorly on a wide range of achievement tests, and an evaluation of 110 long-term survivors (tested as young adults) showed that cranial radiotherapy was associated with greater psychological stress, worse body image, and poor academic achievement. These findings were important to defining the potential long-term ramifications of cranial radiotherapy for childhood ALL, and in the interim, more efficacious chemotherapy regimens directed toward the central nervous system have been established, such that the majority of children with ALL no longer require cranial radiotherapy (11).

Extended field radiotherapy for Hodgkin’s disease. CALGB 6604 was the first multicenter cooperative group randomized study testing the concept of extended field radiotherapy for Hodgkin’s disease (12). This trial included 123 patients randomized to receive either chemotherapy, chemotherapy followed by involved field radiotherapy, chemotherapy followed by total nodal radiotherapy, total nodal radiotherapy followed by chemotherapy, or total nodal radiotherapy alone. This was also one of the first trials to incorporate specific requirements for radiotherapy, including the use of cobalt teletherapy, or its equivalent, as well as the requirement for portal film localization for each field treated. Radiotherapy doses ranged from 3,000 cGy to uninvolved regions up to 4,000 cGy for areas of known disease. Although no definitive conclusions could be reached about optimal therapy due to the small sample size in this trial, meaningful observations were made with regard to patterns of failure among the treatment groups: relapse in initially involved lymph nodes was much less common in patients receiving radiotherapy compared with chemotherapy alone. The critical importance of radiotherapy technique was also shown, as four patients developed radiation myelitis.

Second malignant neoplasms following radiotherapy for Hodgkin’s disease. CALGB did a pooled analysis of 1,332 patients treated on four Hodgkin’s disease trials between 1966 and 1974 (13). This study population consisted of 798 patients who achieved complete remission, including 369 patients who never received radiotherapy. This analysis did not reveal an increase in incidence of acute myeloid leukemia with the addition of radiotherapy regardless of extent of treatment (involved field versus extended field versus total nodal radiotherapy). However, radiotherapy was found to be a significant factor in the development of second malignancies other than acute myeloid leukemia for a standardized risk ratio of 3.3. Additional important observations included the appearance of solid malignancies in patients with sustained complete response beyond 7 years, with the acknowledgement that the expression of this risk might not be appreciated for another decade. In addition, younger patients were found to be at higher risk for secondary malignancies. These observations helped strengthen the notion that future strategies for Hodgkin’s disease should be aimed at delivering tailored therapy that would result in durable disease control while reducing the risk of secondary malignancies.

Studies assessing radiotherapy timing

The optimal timing for administering radiotherapy relative to systemic chemotherapy remains an important and highly debated topic. Several CALGB studies have provided data to help address this issue.

Timing of thoracic radiotherapy in LSCLC. CALGB 8083 randomly assigned patients to receive initial radiotherapy plus chemotherapy, delayed radiotherapy plus chemotherapy, or chemotherapy alone (14, 15). The chemotherapy consisted of cyclophosphamide, etoposide, and vincristine, with doxorubicin substituting for etoposide during later cycles. Radiotherapy, 50 Gy in 5 weeks, was administered with the first (early) or...
fourth cycle (delayed) of chemotherapy. Overall, 399 patients were evaluable. Survival with chemotherapy alone was inferior to both radiotherapy arms, and the difference was statistically significant for delayed radiotherapy ($P = 0.002$) and approached significance for early radiotherapy ($P = 0.082$). No significant difference was observed between early and delayed radiotherapy, although there was a trend favoring delayed radiotherapy ($P = 0.14$). The median time to clinical failure was likewise significantly worse with chemotherapy alone than on either radiotherapy arm, and again no difference was observed between radiation arms. The results of this trial provided support for the delayed administration of radiotherapy in LSCLC. Conversely, a phase III trial from the National Cancer Institute of Canada showed a benefit for initiating radiotherapy with the second chemotherapy cycle compared with the sixth cycle of chemotherapy (16). Interestingly, the National Cancer Institute of Canada trial was subsequently repeated by investigators in the United Kingdom who did not confirm a benefit for early radiotherapy (17). Nevertheless, the timing of radiotherapy in LSCLC remains a contentious issue with a recent “meta-analysis” failing to reach a resolution (18). Based on the available evidence, the CALGB has adopted a treatment schema that initiates radiotherapy with the third cycle of chemotherapy for LSCLC.

**Timing of radiotherapy in node-positive breast cancer.** CALGB 9344 tested the benefit of the sequential addition of four cycles of paclitaxel to four cycles of adjuvant doxorubicin and cyclophosphamide in patients with early-stage breast cancer metastatic to axillary lymph nodes (19). The addition of paclitaxel resulted in a significant overall survival advantage compared with doxorubicin and cyclophosphamide alone. Concerns were raised about the potential adverse effect of delaying radiotherapy, given previous observations that chemotherapy administration had little effect on local tumor control. Moreover, a prior CALGB experience in patients with breast cancer metastatic to ≥10 lymph nodes noted that patients receiving more intensive chemotherapy were less likely to initiate and complete radiotherapy (4). Thus, the CALGB Radiation Oncology Committee did a retrospective analysis, including 1,000 patients entered on CALGB 9344 (20). Despite the delay in initiating radiotherapy due to additional chemotherapy in patients randomized to receive paclitaxel, local control was improved compared with doxorubicin and cyclophosphamide alone in patients treated with breast-conserving therapy. Moreover, the addition of paclitaxel did not adversely affect delivery or tolerance of radiotherapy.

**Timing of radiotherapy in locally advanced NSCLC.** Similar to the experience in LSCLC, the question whether radiotherapy should be given at the initiation of chemotherapy or delayed until later in the treatment course (e.g., chemotherapy cycle 3) remains controversial in unresectable stage III NSCLC. The results of CALGB 39801, a phase III trial comparing induction chemotherapy followed by concurrent chemotherapy and radiotherapy with immediate concurrent chemotherapy and radiotherapy, showed that the addition of two cycles of induction paclitaxel and carboplatin chemotherapy did not significantly improve patient outcomes (21). Although the median survival was numerically greater with delayed radiotherapy compared with immediate radiotherapy, 14 months versus 11.4 months, respectively, the difference did not reach statistical significance. Moreover, when the analysis was limited to patients with weight loss <5% (before study entry), the median survival in both arms was similar at 15 months. Thus, patients in the immediate radiotherapy arm did just as well despite receiving less overall therapy. Based on these results, the CALGB has adopted a platform of immediate radiotherapy and concurrent chemotherapy for stage III NSCLC trials.

### Studies of radiation dose modulation

CALGB has been a leader in conducting cooperative group trials assessing high-dose thoracic radiotherapy in both LSCLC and locally advanced NSCLC (Table 1; refs. 7, 8, 22–27).

**Limited small cell lung cancer.** The optimal dose and fractionation of thoracic radiotherapy for LSCLC has not been defined. Although Intergroup trial 0096 showed improved survival with accelerated twice-daily radiotherapy (45 Gy/3 weeks) compared with once-daily radiotherapy (45 Gy/5 weeks), the twice-daily radiotherapy practice has not been widely accepted (28). This may be, in part, due to the increased acute toxicity associated with twice-daily radiotherapy, but the study has also been criticized for the lack of a high-dose once-daily radiotherapy treatment arm. CALGB 8837, a phase I

### Table 1. CALGB trials of high-dose thoracic radiotherapy in lung cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Disease</th>
<th>$n$</th>
<th>Thoracic radiotherapy</th>
<th>Chemotherapy</th>
<th>Year completed</th>
</tr>
</thead>
<tbody>
<tr>
<td>8837 Phase I (22, 27)</td>
<td>LSCLC</td>
<td>47</td>
<td>56-70 Gy once daily/ 45-55 Gy twice daily</td>
<td>Cisplatin, cytoxan, and etoposide</td>
<td>1994</td>
</tr>
<tr>
<td>39808 Phase II (23)</td>
<td>LSCLC</td>
<td>75</td>
<td>70 Gy once daily</td>
<td>PdT</td>
<td>2000</td>
</tr>
<tr>
<td>30002 Phase II (24)</td>
<td>LSCLC</td>
<td>65</td>
<td>70 Gy once daily</td>
<td>EPdT</td>
<td>2003</td>
</tr>
<tr>
<td>30202 (RTOG 0241) phase I (25)</td>
<td>LSCLC</td>
<td>36</td>
<td>70 Gy once daily/ 45 Gy twice daily</td>
<td>PIV</td>
<td>2005</td>
</tr>
<tr>
<td>30105 Randomized phase II (7)</td>
<td>NSCLC</td>
<td>69</td>
<td>74 Gy once daily</td>
<td>GCb PxCb</td>
<td>2004</td>
</tr>
<tr>
<td>30206 Phase II (26)</td>
<td>LSCLC</td>
<td>78</td>
<td>70 Gy once daily</td>
<td>PIV</td>
<td>2005</td>
</tr>
<tr>
<td>30407 Randomized phase II (8)</td>
<td>NSCLC</td>
<td>100</td>
<td>70 Gy once daily</td>
<td>PmPxC</td>
<td>2005</td>
</tr>
</tbody>
</table>
Radiation and CALGB

Studies assessing novel combinations of radiotherapy and systemic therapy

Many newer generation systemic chemotherapy agents show specific radiosensitizing properties in preclinical or early clinical trials. A major theme of CALGB studies in both respiratory and gastrointestinal malignancies has been to test the hypothesis that combining these agents with radiotherapy will improve treatment efficacy.

Gastrointestinal malignancies

**Anal carcinoma.** Organ preservation with chemoradiotherapy has long been considered as the standard approach for localized carcinoma of the anal canal. Initial studies in the 1970s showed impressive tumor regression when radiotherapy was given simultaneously with 5-fluorouracil (5-FU) and mitomycin-C, and subsequent trials documented that combined modality therapy could provide long-term tumor control without the need for surgery in the majority of patients (34, 35). The high rate of severe acute toxicity, coupled with suboptimal results in locally advanced disease, led to a search for a regimen with an improved therapeutic index. CALGB 9281, a phase II trial in high-risk carcinoma of the anal canal, assessed the role of cisplatin as both a systemic agent and a radiosensitizer (36). Cisplatin was given with 5-FU and radiotherapy during the "boost" portion of treatment for patients with residual tumor. This regimen was tolerable and showed an encouraging 67% disease-free survival in patients with locally advanced disease. CALGB 9281, in conjunction with other clinical experience (37, 38), provided background data for the recently completed phase III Intergroup study comparing cisplatin with mitomycin-C, each given with 5-FU, in locally advanced anal carcinoma (39).

**Rectal cancer.** Oxaliplatin is a novel platinum analogue that has improved the efficacy of systemic therapy in metastatic colorectal cancer (40). The agent is more active than cisplatin in vitro and has potent radiosensitizing properties. CALGB 89901, a phase I/II trial, assessed preoperative oxaliplatin concurrent with 5-FU and radiotherapy for locally advanced (T3 and T4) rectal cancer (41). The maximum tolerated dose of oxaliplatin was determined to be 60 mg/m² when administered with infusional 5-FU and radiotherapy. Encouraging activity was observed with this combination, including 25% pathologic complete response in patients enrolled at the phase II dose. The regimen of radiotherapy plus oxaliplatin and infusional 5-FU, as piloted by the CALGB, is now being evaluated in a phase III Intergroup rectal cancer trial (42).

**Pancreatic cancer.** CALGB trials in locally advanced pancreatic cancer have focused on integrating gemcitabine with radiotherapy. Gemcitabine chemotherapy is the standard of care for metastatic pancreatic cancer and an agent with potent radiosensitizing properties (43). The results of sequential phase II CALGB studies suggest improved efficacy with the addition of gemcitabine to radiotherapy and infusional 5-FU (CALGB 80003) but not with the substitution of gemcitabine for 5-FU during radiotherapy (CALGB 89905; refs. 44, 45). Despite initial concerns about the potential toxic effects of double radiosensitization on CALGB 80003, unexpectedly high rates of severe acute toxicity were not observed. An emphasis on conformal radiotherapy techniques may have allowed for the potentially more toxic combination therapy to be given safely, and future efforts will build on this experience.

Non–small cell lung cancer

Several CALGB trials have included an assessment of the potential radiosensitizing activity of newer generation systemic...
radiotherapy with weekly paclitaxel (50 mg/m²) and carboplatin chemotherapy followed by 66 Gy. Patients treated on CALGB 9534 received two cycles of induction chemotherapy agents in locally advanced NSCLC. CALGB 9130 randomized patients to receive two cycles of induction cisplatin and vinblastine chemotherapy followed by radiotherapy alone (60 Gy/6 weeks) or the same induction regimen followed by radiotherapy with weekly carboplatin (100 mg/m²; ref. 46). This trial followed a European study that reported improved survival, due to better local tumor control, when daily cisplatin was administered during radiotherapy for locally advanced NSCLC (47). Although local tumor control was superior with weekly carboplatin, this did not translate into better survival in the CALGB experience. A subsequent randomized phase II trial, CALGB 9431, sought to improve outcomes through administration of more intensive doses of newer generation chemotherapy drugs during radiotherapy (48). Two cycles of gemcitabine, paclitaxel, and vinorelbine, in combination with cisplatin, were followed by two additional cycles concurrently with radiotherapy (66 Gy/33 fractions). The median survival for the gemcitabine, paclitaxel, and vinorelbine arms were 18.3, 14.8, and 17.7 months, respectively. Although these results eclipsed prior CALGB trials of sequential therapy, the therapeutic index of these regimens, compared with trials of radiotherapy with previous generation doublet chemotherapy, did not warrant proceeding with phase III studies (49).

The CALGB contemporaneously conducted the first cooperative group phase II study of radiotherapy concurrently with weekly paclitaxel and carboplatin chemotherapy in stage III NSCLC (50). This regimen had rapidly been adopted in clinical practice as one of the most commonly used treatments for unresectable NSCLC following the publication of several prospective studies in the early to mid 1990s that suggested excellent survival and little severe toxicity (51, 52). Forty-one patients treated on CALGB 9534 received two cycles of induction paclitaxel and carboplatin chemotherapy followed by 66 Gy radiotherapy with weekly paclitaxel (50 mg/m²) and carboplatin (area under the curve = 2). The most common severe toxicity during combined modality therapy was esophagitis, which was observed in 35% of patients, and median survival was 14.5 months. CALGB 39801, a subsequent phase III study assessing the role of induction chemotherapy, used the same regimen piloted in CALGB 9534 as the experimental arm, and similar outcomes were observed (14-month median survival). The disappointing results of these studies have called into question the routine use of radiotherapy with weekly paclitaxel and carboplatin in clinical practice and resulted in a shift to assessing full doses of systemic chemotherapy during radiotherapy in CALGB trials.

**Special populations**

**Breast-conserving radiotherapy in the elderly population.** The mature results of large randomized phase III trials in early-stage breast cancer have documented a significant reduction of recurrent tumor in the ipsilateral breast when breast radiotherapy is administered after lumpectomy compared with lumpectomy without radiotherapy (53, 54). However, breast cancer tends to be less aggressive in elderly women with a lower risk of ipsilateral breast recurrence compared with younger patients. CALGB 9343 was a unique phase III study assessing the role of breast radiotherapy in the elderly population (55). Patients, ages ≥70 years and with early-stage estrogen receptor-positive breast cancer, were randomized to receive tamoxifen and radiotherapy following lumpectomy. The 5-year rate of local or regional recurrence was 1% in patients treated with radiotherapy and tamoxifen compared with 4% in patients who did not receive radiotherapy (P < 0.001). As expected, no difference in survival was observed between treatment arms. This study provides unique data to help guide treatment decisions for elderly patients with early-stage estrogen receptor-positive breast cancer.

**Medically inoperable early-stage NSCLC.** Although the majority of patients with stage I NSCLC may be cured following anatomic resection (e.g., lobectomy), a substantial portion have cardiopulmonary dysfunction or other medical comorbidity, rendering them ineligible for major surgery (56). CALGB conducted the initial cooperative group studies designed specifically for high-risk patients with early-stage NSCLC. CALGB 9335 examined a plan of video-assisted thoracoscopic wedge resection followed by external beam radiotherapy for stage IA NSCLC (57). Radiotherapy was well tolerated, with a low risk of pulmonary toxicity. In contrast to excellent results from single-institution experience of wedge resection in high-risk patients, <30% of patients on CALGB 9335 remained alive 5 years following treatment (58, 59). This trial called into question the role of surgical resection in the high-risk population, and a recently completed trial, CALGB 39904, assessed dose-intensive accelerated three-dimensional conformal radiotherapy in a similar population (60). The radiotherapy schedule was reduced from 28 fractions in 5.5 weeks to 17 fractions in 3.5 weeks while maintaining a nominal total dose of 70 Gy. Follow-up is still short, but dose-limiting toxicity has not been observed. These trials will help guide treatment decisions for a population that will likely continue to increase in the future.

**Conclusion**

CALGB initiatives have significantly affected cancer care and the practice of radiation oncology during the past several decades. Critical issues about the appropriate integration of radiotherapy into overall treatment have been studied, whereas ongoing efforts continue to emphasize the goal of enhancing tumor control and patient outcomes through the safe administration of intensive therapy. The emergence of new technologies for planning and delivering radiotherapy, coupled with a growing understanding of underlying tumor biology, will result in increased opportunities for high-effect radiotherapy cooperative group research in the years to come.

**References**


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