Radiation Treatment Breaks and Ulcerative Mucositis in Head and Neck Cancer

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ABSTRACT
Unplanned radiation treatment breaks and prolongation of the radiation treatment time are associated with lower survival and locoregional control rates when radiotherapy or concurrent chemoradiotherapy is used in the curative treatment of head and neck cancer. Treatment of head and neck cancer is intense, involving high-dose, continuous radiotherapy, and often adding chemotherapy to radiotherapy. As the intensity of treatment regimens has escalated in recent years, clinical outcomes generally have improved. However, more intensive therapy also increases the incidence of ulcerative mucositis, thereby increasing the incidence of unplanned radiation treatment breaks. Conversely, the reduction of ulcerative mucositis to minimize unplanned breaks in radiotherapy may enhance not only tolerability, but also efficacy outcomes. Several strategies to prevent ulcerative mucositis in radiotherapy for head and neck cancer have been evaluated, but none have demonstrated strong efficacy. Continued investigation is needed to identify superior radiation treatment regimens, technology, and supportive care that reduce unplanned radiation treatment breaks with the goal of improving clinical outcomes in head and neck cancer. The Oncologist 2008;13:886–898

INTRODUCTION
Squamous cell carcinoma of the head and neck occurs in a substantial number of patients: projections for 2007 in the U.S. alone included approximately 45,660 new cases and 11,210 deaths for cancer of the oral cavity, pharynx, and larynx [1]. Patients who present with local disease are typically treated with a single-modality approach using surgery or radiotherapy. However, approximately 65% of
patients with head and neck tumors present with locally advanced disease [2], which typically requires a multidisciplinary approach [2–7].

Concurrent chemoradiotherapy (CRT) can result in a superior treatment response and survival outcome compared with radiotherapy alone in these patients [3], and it has become the standard of care for locally advanced disease and organ preservation. However, 3 years after concurrent CRT, 30%–40% of patients will experience locoregional recurrences, and 20%–30% will develop distant metastases [3–6]. Additionally, the combination of chemotherapy and radiotherapy may improve survival to a lesser extent than it improves local treatment response and control, while adding to acute toxicity [4, 5].

The major limitation to continuous, uninterrupted radiotherapy and concurrent CRT in the management of head and neck cancer is ulcerative mucositis. Unplanned radiation treatment breaks resulting from ulcerative mucositis and the associated acute side effects negatively impact treatment outcomes for many types of tumors, but the detrimental effect appears greatest in head and neck cancer [4]. Ulcerative mucositis is difficult to assess because it occurs not only in the oral cavity but also in areas that cannot be easily observed, such as the esophagus and hypopharynx. The secondary acute effects of oral mucositis include acute and chronic aspiration, inanition, infection, and severe pain. These lead to significant morbidity requiring treatment interruptions.

The objective of this article is to review data on the clinical consequences of radiation treatment breaks, the association between ulcerative mucositis and radiation treatment breaks, and possible strategies to prevent radiation treatment breaks by reducing ulcerative mucositis in the management of head and neck cancer. A literature search (published from the year 2000 to the present) was performed in the MEDLINE, Embase, Biosis, Ovid Journals Full Text, and Conference Papers Index databases. The search strategy consisted of text words and synonyms for treatment breaks, survival analysis, treatment outcomes, radiotherapy, chemotherapy, breast cancer, head and neck cancer, lung cancer, colorectal cancer, and hematological neoplasm. Literature references were selected by the authors on the basis of their relevance to current clinical practice for the treatment of head and neck cancer.

**BILOGIC CONSEQUENCES OF RADIATION TREATMENT BREAKS**

Studies in radiation biology have demonstrated that there is a higher risk for proliferation by residual tumor cells when local radiotherapy is delayed or interrupted. The biological basis for the negative effects of unplanned radiation treatment breaks on clinical outcomes has been attributed to tumor stem cells, cells that can reproduce indefinitely and can therefore cause recurrence [6]. In contrast, most cells in a tumor have a limited life span. Approximately 2–4 weeks after the initiation of radiotherapy, surviving tumor stem cell repopulation in head and neck cancer accelerates and occurs continually during radiation [6, 7]. The accelerated repopulation by tumor stem cells is a consequence of radiotherapy-induced killing of tumor cells; the surviving cells cycle faster during the time the radiation is not being applied. Additionally, surgery interrupting radiotherapy may trigger accelerated tumor regression by enhancing the growth environment during healing. The molecular mechanisms underlying accelerated repopulation by tumor cells receiving sublethal doses of radiotherapy likely involve pre-existing signal transduction pathways that have the potential to stimulate cellular proliferation [8].

During accelerated repopulation, the estimated tumor stem cell doubling time may shorten from approximately 60 days to 4 days [6]. Tarnawski et al. [7] retrospectively estimated repopulation rates for 1,502 patients with carcinoma of the larynx or pharynx who were treated with radiotherapy alone. The probability of tumor control significantly correlated with radiation dose, tumor–node–metastasis stage, overall radiation treatment time, and gap duration. Ninety percent of these patients had unplanned radiation treatment breaks (mean break of 9 days), and accelerated repopulation of tumor cells occurred more rapidly during a break than during normal days of radiotherapy. During the radiation treatment break, the proliferation rate was equal to 0.75 cell doubling per day versus 0.2 cell doubling per day during days with irradiation, which means that the clonogens are capable of proliferating three times faster on days when no radiotherapy is given than on days when radiotherapy is given. This higher rate strongly demonstrates the cellular basis for the impact of planned and unplanned radiation treatment delays on locoregional control, as confirmed in clinical studies.

**CLINICAL CONSEQUENCES OF RADIATION TREATMENT BREAKS**

Studies quantifying the adverse clinical consequences of unplanned radiation treatment breaks—and the resulting prolongation of the overall radiation treatment time—are summarized in Table 1 [9–21]. Unplanned breaks in radiotherapy for head and neck cancer are associated with significantly worse locoregional control [10, 11, 13]. There is evidence that even a short break may have negative conse-
Table 1. Radiotherapy: effects of unplanned radiation treatment breaks and prolonged radiation treatment time on efficacy outcome

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>n of patients</th>
<th>Efficacy outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unplanned radiation treatment breaks</td>
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</tr>
<tr>
<td>Herrmann et al. (1994) [9]</td>
<td>RT (63% postoperative, 37% as primary treatment)</td>
<td>192</td>
<td>LRC closely correlated with survival: 95% of deaths within 5 yrs were from recurrent carcinoma; breaks in RT resulted in lower 5-yr survival rate ($p &lt; .001$); no breaks, 61% survival rate; breaks during first 3 wks, 65% survival rate; breaks during middle 2 wks, 25% survival rate; breaks during last 2 wks, 18% survival rate</td>
</tr>
<tr>
<td>Robertson et al. (1998) [10]</td>
<td>RT was primary treatment for all patients; 3% had prior surgery</td>
<td>352</td>
<td>Breaks of ≥3 days resulted in poorer local control relative to no breaks (HR, 1.75; 95% CI, 1.20–2.55); position of breaks did not matter</td>
</tr>
<tr>
<td>Robertson et al. (1998) [11]</td>
<td>RT (various schedules)</td>
<td>2,225 (retrospective, 4 institutions)</td>
<td>Break or prolongation by 1 day associated with lower 2-yr local control rate by 0.68% per day</td>
</tr>
<tr>
<td>Suwinski et al. (2003) [12]</td>
<td>Postoperative RT</td>
<td>868 (retrospective)</td>
<td>Breaks &lt;6 days did not influence RFS; longer breaks were associated with ~1%–2% lower RFS rate per day</td>
</tr>
<tr>
<td>Groome et al. (2006) [13]</td>
<td>&gt;90% received RT alone as initial therapy</td>
<td>491 stage T1N0; 213 stage T2N0 (population-based)</td>
<td>Local failure associated with stage T1N0 disease: ≥4 RT interruption days—RR, 2.43; 95% CI, 1.00–5.91; stage T2N0 disease: late RT breaks (i.e., after day 28)—RR, 2.19; 95% CI, 1.09–4.41</td>
</tr>
<tr>
<td>Overall radiation treatment time</td>
<td></td>
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<tr>
<td>Barton et al. (1992) [14]</td>
<td>Definitive RT for larynx carcinoma</td>
<td>1,012 (retrospective)</td>
<td>OTT significantly affected local control ($p = .02$ when adjusted for influence of stage and laryngeal subsite); hazard of local relapse 4.8% higher per day of interruption ($p = .006$), resulting in lower local control rate by 1.4% per day if uncompensated</td>
</tr>
<tr>
<td>Fowler et al. (1992) [15]</td>
<td>RT</td>
<td>3,834 (literature review, 12 reports)</td>
<td>OTT correlated with local control ($p &lt; .05$ for 10 of 12 reports); median loss of local control was 14% per wk (range, 3%–25%)</td>
</tr>
<tr>
<td>Withers et al. (1995) [16]</td>
<td>RT (various dose fractionation patterns)</td>
<td>676 (retrospective)</td>
<td>Tumor control probability ≥1% lower per day with longer OTT</td>
</tr>
</tbody>
</table>

(continued)
quences; in a retrospective analysis of 2,225 patients from four centers [11], an unplanned break of only 1 day resulted in a 0.68% lower 2-year local control rate. Other authors have estimated that the tumor control rate is at least 1% lower for every day that radiation treatment is interrupted [4, 6]. Unplanned breaks, especially those of several days or more, also have been reported to result in significantly shorter overall survival [9] and relapse-free survival [12] times. After radiotherapy is held for 6 days, every additional day is associated with a 1%–2% lower 5-year relapse-free survival rate [12].

Indirect evidence of the negative consequences of unplanned radiation treatment breaks comes from several studies of total radiation treatment time. Unintended prolongation of the total time of definitive radiotherapy is associated with worse locoregional control [14–16, 18] and survival [12, 17]. In the case of postoperative treatment of head and neck cancer, there can be significant delays in the “package time”—the time from surgery to completion of postoperative radiotherapy. The 5-yr actuarial LRC rate for package time <11 wks was 76%, compared with 62% for 11–13 wks and 38% for >13 wks (p = .002); the 5-yr survival rate for package time <11 wks was 48%, compared with 27% for 11–13 wks and 25% for >13 wks (p = .003).

Table 1. (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>n of patients</th>
<th>Efficacy outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alden et al. (1996) [17]</td>
<td>Induction CT (5-FU + cisplatin); definitive RT-std</td>
<td>41</td>
<td>Elapsed RT treatment time was highly predictive of survival (p = .02); 5-yr rates (median times): RT &lt;55 days, 56% (98 mos); RT 56–65 days, 46% (57 mos); RT &gt;66 days, 15% (15 mos)</td>
</tr>
<tr>
<td>Rosenthal et al. (2002) [18]</td>
<td>Postoperative RT</td>
<td>208 (retrospective)</td>
<td>RT treatment time was associated with locoregional failure (p = .03)</td>
</tr>
<tr>
<td>Suwinski et al. (2003) [12]</td>
<td>Postoperative RT</td>
<td>868 (retrospective)</td>
<td>Prolongation of RT treatment time by 10 days was related to a 10%–20% lower 5-yr RFS rate</td>
</tr>
</tbody>
</table>

Package time (time between surgery and completion of radiotherapy)

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>n of patients</th>
<th>Efficacy outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parsons et al. (1997) [19]</td>
<td>Postoperative RT</td>
<td>134</td>
<td>Unfavorable tumors (≥4 indications for RT and/or invasive at margins): LRC higher for package time ≥100 days (60% versus 14%; p = .04); favorable tumors: no significant effect of package time on LRC</td>
</tr>
<tr>
<td>Ang et al. (2001) [20]</td>
<td>Postoperative RT delivered in 5 versus 7 wks</td>
<td>151 high-risk patients</td>
<td>The 5-yr actuarial LRC rate for package time &lt;11 wks was 76%, compared with 62% for 11–13 wks and 38% for &gt;13 wks (p = .002); the 5-yr survival rate for package time &lt;11 wks was 48%, compared with 27% for 11–13 wks and 25% for &gt;13 wks (p = .003)</td>
</tr>
<tr>
<td>Rosenthal et al. (2002) [18]</td>
<td>Surgery plus postoperative RT</td>
<td>208 (retrospective)</td>
<td>Package time associated with locoregional failure (p = .13); package time predicted survival (p = .021)</td>
</tr>
</tbody>
</table>

Abbreviations: 5-FU, 5-fluorouracil; CI, confidence interval; HR, hazard ratio; LRC, locoregional control; N, node stage; OTT, overall treatment time; RFS, recurrence-free survival; RR, relative risk; RT, radiotherapy; RT-std, standard radiotherapy; T, tumor stage.
during planned treatment breaks—alternating chemotherapy and radiation therapy—can minimize the “time factor” found to be so critical. In a phase III study from Italy that randomized patients between standard radiation therapy and alternating chemotherapy and radiation therapy (three cycles of cisplatin plus 5-fluorouracil [5-FU] alternating with three 2-week courses of standard fractionated radiation therapy), the patients in the combination therapy arm had superior response, 3-year and 5-year survival, disease-free survival, and local control rates, and there was no difference in the acute high-grade mucositis rates [22, 23]. The total treatment time for the alternating chemotherapy and radiation therapy arm was 10 weeks. This suggests that the adverse effect of a longer treatment time may be less relevant when additional negative growth pressure (i.e., chemotherapy) is applied to tumor clonogens during breaks, and permit healing of normal tissues.

**Radiation Treatment Breaks and Altered Fractionation Schedules**

Just as unplanned radiation treatment breaks are known to have clinical consequences, planned radiation treatment breaks may explain some of the observed results in controlled clinical trials of altered fractionation schedules (Table 2) [24–31]. Planned radiation treatment breaks have the potential benefit of improving radiation tolerability and quality of life by reducing mucositis and its consequences, but they may come at the expense of poorer tumor control.

In an early controlled study of altered fractionation for head and neck cancer [24], hyperfractionation (1.15 Gy twice daily, 5 days/week for 7 weeks) was well tolerated and resulted in significantly better locoregional tumor control, but was not associated with a statistically significant survival benefit compared with standard radiotherapy (2.0 Gy once daily, 5 days/week for 7 weeks).

A subsequent larger randomized phase III study [25] in 1,073 patients with head and neck cancer compared standard once-a-day radiotherapy (2.0 Gy once daily, 5 day/week for 7 weeks), hyperfractionation (1.2 Gy twice daily, 5 days/week for 7 weeks), accelerated hyperfractionation with a break (1.6 Gy twice daily, 5 days/week for 6 weeks including a 2-week rest after 38.4 Gy), and accelerated fractionation with a concomitant boost (1.8 Gy once daily, 5 days/week for 6 weeks, plus an additional 1.5 Gy once daily to a boost field during the last 12 radiation treatment days). Hyperfractionation and accelerated fractionation with a concomitant boost resulted in better locoregional tumor control but did not alter survival significantly. The combination of accelerated hyperfractionation with a break did not affect locoregional tumor control or survival outcomes when compared with the standard treatment arm—once-daily, standard fractionated radiotherapy. This finding may have been a result of the inclusion of the planned 2-week break, which appears to negate the benefits of hyperfractionation and acceleration. Support for this theory comes from a secondary analysis of 501 patients treated with split-course (n = 191) or continuous (n = 310) radiotherapy in two randomized trials of the Danish Head and Neck Cancer Group [32], in which the overall 5-year locoregional control rate was lower for split-course radiotherapy (30% versus 41%; p = .007), particularly among well-differentiated tumors (21% versus 38%; p = 0.011; Fig. 1).

Conversely, reducing or eliminating planned radiation treatment breaks and reducing the overall treatment time has been shown to lead to better tumor control. Overgaard et al. [26] demonstrated that administration of a sixth weekly dose, either alone on day 6 or as a second dose on day 5, and reducing the total radiation treatment time from 6.5 to 5.5 weeks resulted in better locoregional tumor control; however, it did not affect survival and it resulted in a higher incidence of acute morbidity (Fig. 2).

Maciejewski et al. [33] eliminated all treatment breaks and administered standard fractionated radiotherapy 7 days a week for five consecutive weeks in a noncontrolled study; however, this regimen resulted in unacceptable acute morbidity and consequential late morbidity. By using the 7 days/week schedule for 5 weeks but decreasing the daily dose from 2.0 Gy to 1.8 Gy in a small controlled trial [27, 28], the investigators were able to reduce morbidity to a manageable level and demonstrated a highly significant greater 5-year locoregional tumor control rate of 75% for continuous accelerated irradiation, versus 33% with standard fractionation. One approach that has been examined in clinical trials is the use of short-course, continuous hyperfractionated accelerated radiotherapy (CHART), whereby 36 fractions of radiotherapy are administered three times daily for 12 consecutive days (compared with 5–7 weeks of therapy for most radiotherapy regimens). In the initial report of a multicenter comparison of CHART and conventional radiotherapy in 918 patients, the locoregional tumor control rate was comparable between the radiation treatments, but late radiation morbidity favored CHART [29]. However, a subsequent analysis of data from the study [34] reported that CHART was associated with a greater incidence (75% versus 44%) and peak prevalence (60% versus 34%) of confluent ulcerative mucositis. Highly significant relationships between ulcerative mucositis grade and dysphagia, odynophagia, and prescribed narcotics were also observed.

Two meta-analyses of randomized altered fractionation trials [30, 31] addressed the relative efficacy of accelerated versus hyperfractionated schedules. Both meta-analyses demonstrated significantly longer survival times for hyperfractionated radiotherapy relative to accelerated radiothera-
Table 2. Selected randomized trials and meta-analyses of altered fractionation schedules: efficacy and toxicity outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>n of patients</th>
<th>Efficacy outcome</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horiot et al. (1992)</td>
<td>RT-std or RT-hf</td>
<td>356</td>
<td>5-yr local control rate was better with RT-hf (59% versus 40%; ( p = .02 )); trend toward longer survival with RT-hf (( p = .08 ))</td>
<td>Grade 3 diffuse ulcerative mucositis: RT-std, 49%; RT-hf, 66.5%; no difference in late effects</td>
</tr>
<tr>
<td>Fu et al. (2000)</td>
<td>RT-std, RT-hf, RT-accel (split), or RT-accel (boost)</td>
<td>1,073</td>
<td>RT-hf and RT-accel (boost) associated with better LRC (( p = .045 ) and ( p = .050 )) compared with RT-std; no significant differences in OS among regimens; RT-hf and RT-accel (boost) trend toward higher DFS rate (( p = .067 ) and ( p = .054 )) relative to RT-std</td>
<td>Grade 3+ mucous membrane toxicity: RT-std, 25%; RT-hf, 42%; RT-accel (boost), 47%; RT-accel (split), 41%; no significant difference in late effects</td>
</tr>
<tr>
<td>Overgaard et al. (2003)</td>
<td>RT-6 or RT-std</td>
<td>1,476</td>
<td>5-yr LRC rate, 70% for RT-6 and 60% for RT-std (( p = .0005 )); DFS rate, 73% for RT-6 and 66% for RT-std (( p = .01 ))</td>
<td>Confluent ulcerative mucositis, 53% versus 33% (( p &lt; .0001 ))</td>
</tr>
<tr>
<td>Skladowski et al. (2000, 2006)</td>
<td>CAIR or RT-std</td>
<td>100</td>
<td>3-yr local control rate, 82% for CAIR versus 37% (( p &lt; .0001 )); 5-yr local control rate, 75% for CAIR versus 33% (( p &lt; .00004 )); actuarial 3-yr OS rate, 78% for CAIR versus 32% (( p &lt; .0001 )); 5-yr OS rate for CAIR also better (( p = .00005 ))</td>
<td>Confluent ulcerative mucositis occurred more often with CAIR (94% versus 53%; ( p &lt; .00001 )) and had a longer duration (mean, 4.2 versus 1.5 wks)</td>
</tr>
<tr>
<td>Dische et al. (1997)</td>
<td>CHART or RT-std</td>
<td>918</td>
<td>No difference between the arms in LRC, primary tumor control, nodal control, disease-free interval, metastasis-free survival, and overall survival; CHART was more effective in younger patients (( p = .041 )); RT-std was more effective for poorly differentiated tumors (( p = .030 ))</td>
<td>Osteoradionecrosis in 0.4% of patients after CHART and 1.4% of patients after conventional radiotherapy; late morbidities were less severe with CHART, but acute ulcerative mucositis was more severe and started earlier</td>
</tr>
<tr>
<td>Bourhis et al. (2006)</td>
<td>RT-std, RT-accel, or RT-hf</td>
<td>6,515 (15 trials)</td>
<td>LRC benefit (6.4% at 5 yrs; ( p &lt; .0001 )) favored RT-accel/RT-hf; absolute overall 5-yr survival benefit versus RT-std of 8% for RT-hf, ~2% for RT-accel</td>
<td>—</td>
</tr>
<tr>
<td>Budach et al. (2006)</td>
<td>RT-std or RT-accel</td>
<td>4,702 (9 trials)</td>
<td>No survival benefit for RT-accel in 8/9 studies; overall, no OS benefit for RT-accel</td>
<td>—</td>
</tr>
<tr>
<td>Budach et al. (2006)</td>
<td>RT-std or RT-hf</td>
<td>1,523 (4 trials)</td>
<td>RT-hf provided OS benefit of 14.2 mos (95% CI, 10.2–18.5; ( p &lt; .0001 ))</td>
<td>—</td>
</tr>
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</table>

Abbreviations: CAIR, continuous accelerated irradiation for 7 days/week; CHART, continuous hyperfractionated accelerated radiotherapy; CI, confidence interval; DFS, disease-free survival; LRC, locoregional control; OS, overall survival; RT, radiotherapy; RT-6, standard radiotherapy plus a sixth dose on Friday or Saturday; RT-accel, accelerated fractionation radiotherapy; RT-alt, altered fractionation; RT-hf, hyperfractionated radiotherapy; RT-std, standard radiotherapy.
apy. However, the authors noted that the modest benefits of most altered radiotherapy schedules may be offset by higher incidences of acute and chronic radiation treatment–related morbidity.

RADIATION TREATMENT BREAKS AND CONCURRENT CRT

The addition of concurrent chemotherapy to radiotherapy has been shown to lead to better organ preservation, locoregional control, and survival in randomized trials and meta-analyses in head and neck cancer [31, 35–43], but not surprisingly, the combination therapy resulted in greater toxicity (Table 3). For example, in the Intergroup phase III trial of unresectable head and neck cancer [35], standard radiation was compared with two different CRT regimens: bolus cisplatin with continuous radiotherapy and a split course with cisplatin plus 5-FU. The bolus cisplatin regimen resulted in significantly better locoregional tumor control and a longer overall survival time compared with radiotherapy alone; split-course treatment (despite having more aggressive chemotherapy) was not statistically different from radiotherapy alone. The survival rate at 3 years was 23%, 27%, and 37%, respectively, for radiotherapy alone, split-course CRT, and continuous CRT with bolus cisplatin, but rates of grade ≥3 toxicity in the CRT groups were significantly greater (52%, 77%, and 89%, respectively).

In contrast to the body of data delineating the negative consequences of radiation treatment breaks and longer total radiation treatment times in radiotherapy alone for head and neck cancer, there is a paucity of data regarding the influence of the radiation treatment time on outcomes when concurrent CRT is used.

The influence of the overall radiation time was specifically evaluated in 88 patients undergoing definitive CRT for head and neck cancer [44]. Patients were treated with two cycles of induction chemotherapy (cisplatin and 5-FU) followed by concurrent CRT with cisplatin and 5-FU in conjunction with once-daily radiotherapy to a planned total dose of 66–74 Gy. After 2 years, the 61 patients with overall radiation times ≥60 days had significantly better local control (89% versus 59%; p = .04) and neck control (95% versus 72%; p = .02) than the 27 patients with overall radiation times <60 days. Likewise, Keane et al. [45] reported the results of a randomized trial involving 212 patients treated with either concurrent chemotherapy (mitomycin C and 5-FU) and 50 Gy radiotherapy over 28 days with a 4-week rest at the midpoint or radiotherapy alone. After a median follow-up of 4.4 years, no significant differences in the local and regional relapse-free rates or overall survival rate were observed between the CRT arm and radiotherapy alone. These studies provide indirect evidence that prolonged radiation treatment breaks in concurrent CRT regimens, whether planned or unplanned, may decrease the beneficial effect of the addition of chemotherapy to radiotherapy.

The trend has been toward increasing the intensity of chemotherapy in head and neck cancer. Although site-specific information is lacking, supporting data from studies in other types of malignancies (e.g., breast cancer [46, 47] and diffuse large-cell lymphoma [48]) have shown correlations between dose-dense chemotherapy and survival. Dose-dense chemotherapy delivers the same dose of chemotherapy at more frequent time intervals, thus reducing the overall time of...
chemotherapy delivery. Biologically, the mechanism may be similar to that of accelerated radiation therapy regimens (i.e., more continuous negative growth pressure on tumor clonogens). Similar correlations might be expected for head and neck cancer. In a report of alternating 1-week cycles of CRT (5-FU and hydroxyurea, with or without cisplatin) with 1-week breaks for tissue recovery in patients with advanced head and neck cancer [49], the authors suggested that the usual association between a longer total radiation treatment time and worse outcomes was not applicable when aggressive cell cycle–specific chemotherapy was given concomitantly with radiotherapy. Among patients who received radiotherapy doses \( \geq 59.4 \text{ Gy} \), local control was achieved in 5 of 17 patients who had failed prior local therapy and 30 of 31 patients with no prior local therapy, despite the longer radiotherapy treatment time, 12–14 weeks total, approximately twice the normal du-

| Table 3. Selected randomized trials and meta-analyses of concurrent chemoradiotherapy versus radiotherapy alone: efficacy and toxicity outcomes |
|---------------------------------|----------------|-----------------
| Study | Regimen | n of patients | Efficacy outcome | Toxicity |
| Adelstein et al. (2003) [35] | A, RT-std; B, RT-std + cisplatin; C, split-course RT + cisplatin and 5-FU | 295 (unreactesetable) | 3-yr projected OS: A, 23%; B, 37% (p < .014 versus A); C, 27% (NS versus A) | Toxicity grade ≥3: A, 52%; B, 89% (p < .001 versus A); C, 77% (p < .001 versus A) |
| Bernier et al. (2004) [36] | A, postoperative RT; B, postoperative RT with concurrent cisplatin | 334 | Estimated 5-yr cumulative incidence of local or regional relapses favored arm B (31% versus 18%; p = .007); survival advantage for arm B after median follow-up of 60 mos—OS: death HR, 0.70; p = .02; PFS: progression HR, 0.75; p = .04 | AEs grade ≥3 more frequent in arm B (41% versus 21%; p = .001); types of severe mucosal AEs and incidence of late AEs similar between arms |
| Brixel et al. (1998) [37] | RT-hf or RT-hf + concurrent PF | 116 evaluable | 3-yr LRC favored PF (70% versus 44%; p = .01); 3-yr OS favored PF (55% versus 34%; p = .07); PF resulted in greater RFS rate (61% versus 41%; p = .08) | Confluent ulcerative mucositis rates were comparable (75% for PF versus 77%) |
| Calais et al. (1999) [38], Denis et al. (2004) [39] | A, RT-std; B, concurrent RT + carboplatin and 5-FU | 226 | 5-yr LRC favored arm B (48% versus 25%; p = .002); 5-yr OS rate favored arm B (22% versus 16%; p = .05); 5-yr DFS rate favored arm B (27% versus 15%; p = .01) | Acute grade 3+ ulcerative mucositis more frequent in arm B (71% versus 39%; p = .005); late grade 3+ effects more common in arm B (56% versus 30%; NS) |
| Cooper et al. (2004) [40] | A, Postoperative RT; B, RT + concurrent cisplatin | 459 | After median follow-up of 45.9 mos, LRC favored group B (HR for recurrence, 0.61; p = .01); OS was not significantly different; DFS time was longer for group B (HR for disease or death, 0.78; p = .04) | Acute grade 3+ AEs higher in arm B (77% versus 34%; p < .001); grade 3+ mucous membrane AEs higher in arm B (62% versus 37%); no significant difference in late effects |
| Forastiere et al. (2003) [41] | A, induction cisplatin + 5-FU followed by RT; B, concurrent cisplatin + RT; C, RT alone | 547 (larynx preservation) | Intact larynx at 2 yrs: A, 75%; B, 88% (p = .005 versus A); C, 70%; local control rate at 2 yrs: A, 64%; B, 80%; C, 58%; OS similar in all 3 groups | Grade 3+ mucosal (stomatitis) effects: A, 24%; B, 43%; C, 24% |
| Staar et al. (2001) [42] | RT-hf (accel) with or without CT (5-FU + carboplatin) | 240 (unreactesetable) | After median 22.9 mos, 1- and 2-yr rates were 69% and 51% (CRT) and 58% and 45% (RT) (p = .05); 1-yr survival with local control (primary endpoint): 58% for CRT versus 44% for RT (p = .05); OS was favored for arm B. (p = .01); OR: for oropharyngeal and NS for hypopharyngeal; 1-yr OS rate of 66% for CRT versus 60% for RT; 2-yr OS rate of 58% for CRT versus 39% for RT | Higher mucosal toxicity after CRT (68% grade 3–4 ulcerative mucositis versus 52%; p = .01); 30% of survivors ≥2 yrs remained dependent on feeding tubes; more patients treated with CRT had swallowing problems and continuous use of feeding tubes (51% versus 25%; p = .02) |
| Budach et al. (2006) [31] | 1A, RT-std with or without concurrent CT; 1B, RT-hf and/or RT-acc with or without concurrent CT; 1C, imbalanced RT regimens with or without concurrent or alternating CT | Meta-analysis: 10 trials (n = 2,197); 6 trials (n = 1,301); 3 trials (n = 502) | OS benefit favored CRT (p < .0001 for all 3 groups); 12.0%, 12.0%, and 7.9-mo benefits for 1A, 1B, and 1C — | — |
| Pigmon et al. (2000) [43] | Locoregional therapy with or without CT (adjuvant, neoadjuvant, or concurrent) | Meta-analysis: 63 trials (n = 10,741) | Absolute OS benefit of 4% at 5 yrs (p < .0001) in favor of CRT; for concurrent CT, absolute OS benefit was 8% at 5 yrs | — |

Abbreviations: 5-FU, 5-fluorouracil; AE, adverse event; CRT, chemoradiotherapy; CT, chemotherapy; HR, hazard ratio; NS, not significant; OS, overall survival; PF, cisplatin/5-fluorouracil; PFS, progression-free survival; RFS, recurrence-free survival; RT, radiotherapy; RT-acc, accelerated fractionation radiotherapy; RT-hf, hyperfractionated radiotherapy; RT-std, standard radiotherapy.

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ration of standard radiotherapy. In a subsequent study that also alternated a week-off/week-on schedule of twice-daily radiotherapy with 5-FU plus hydroxyurea for therapy of stage II–III disease [50], the 3-year overall survival and progression-free survival rates were 78% and 67%, respectively. The intensive chemotherapy, despite the planned breaks, seemed to exert continued negative growth pressure on tumor stem cells and maintain the benefit of the addition of chemotherapy to radiotherapy by allowing for “recovery” of acutely responding tissues during the 1-week interruptions. The drawback to this strategy is that the longer overall radiation treatment time and intensity of the chemotherapy requires that patients be compliant with a very long radiation treatment course, and likely may require multiple hospital admissions. It is not clear that this would be feasible in a less controlled environment. This technique is now being tested in the randomized phase III EPIC multicenter trial in combination with cetuximab [51]. As described previously, outcomes are superior when radiotherapy alone is accelerated on a 7 days/week schedule for a shorter total duration with a lower daily dose [28]. Therefore, the Radiation Therapy Oncology Group (RTOG)-0129 protocol was designed to evaluate the effects of concurrent cisplatin therapy with intensified radiotherapy (70 Gy in 35 fractions given 5 days/week for 7 weeks, versus 72 Gy in 42 fractions given 7 days/week for 6 weeks). That trial has completed accrual, but no efficacy data have yet been reported. If the concurrent CRT regimen using concomitant boost radiotherapy is shown to produce significantly better outcomes, this would provide further support for the importance of minimizing radiation treatment breaks when concomitant chemotherapy is used.

ULCERATIVE MUCOSITIS AND RADIATION TREATMENT BREAKS

The major limitation to more aggressive radiotherapy and concurrent CRT regimens is locoregional treatment-related toxicities, particularly ulcerative mucositis and the consequences of ulcerative mucositis: aspiration, inanition, and severe pain (Table 4) [52, 53]. A literature review conducted by Trotti et al. [52] found that the overall incidence of ulcerative mucositis was 80% among 6,181 patients in 33 studies that used a variety of grading scales; the overall incidence of grade 3–4 ulcerative mucositis was 39%, with incidences of 43% among patients treated with concurrent CRT and 57% among patients treated with altered fractionation schedules. Five of these studies (1,267 patients) specifically evaluated unplanned interruptions/modifications of radiotherapy and found that 11% of patients with mild ulcerative mucositis, 2.4%; among patients with moderate ulcerative mucositis, 15.8%; and among patients with severe ulcerative mucositis, 46.8%, had radiotherapy regimens modified as a result of ulcerative mucositis.

A chart review of 450 patients treated by 154 oncologists [53] confirmed the greater risk for ulcerative mucositis associated with intensified therapy—either concurrent CRT or higher cumulative radiotherapy doses. Unplanned

<table>
<thead>
<tr>
<th>Study population</th>
<th>Incidence of ulcerative mucositis</th>
<th>Incidence of grade 3+ ulcerative mucositis</th>
<th>Weight loss and nutritional support</th>
<th>Hospitalization because of ulcerative mucositis</th>
<th>Incidence of radiation treatment breaks resulting from ulcerative mucositis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systematic analysis of 33 clinical studies (n = 6,181)</td>
<td>RT-std, 97%; CRT, 100%; RT-alt, 89%; CT only, 22%</td>
<td>RT-std, 34%; CRT, 43%; RT-alt, 57%; CT only, 0%</td>
<td>Feeding tube insertion, 19% (reported in 5 studies; n = 819); weight loss, 34% (reported in 8 studies; n = 880); weight loss ≥10%, 17% (reported in 3 studies; n = 485)</td>
<td>RT-std, 5%; CRT, 6%; RT-alt, 32%</td>
<td>Overall, 11% (directly evaluated in 5 studies with 1,267 patients)</td>
</tr>
<tr>
<td>Retrospective analysis of clinical practice (n = 450); 83% RT-std, 16% RT-hf, 33% concurrent CRT</td>
<td>83% ulcerative mucositis overall</td>
<td>29% ulcerative mucositis overall</td>
<td>Insertion of feeding tube/total parenteral nutrition more common among patients with ulcerative mucositis (p = .009)</td>
<td>Hospitalization more common among patients with ulcerative mucositis (p &lt; .001); incidence of hospitalization correlated with severity of ulcerative mucositis</td>
<td>Among patients with mild ulcerative mucositis, 2.4%; among patients with moderate ulcerative mucositis, 15.8%; among patients with severe ulcerative mucositis, 46.8%</td>
</tr>
</tbody>
</table>

Abbreviations: CT, chemotherapy; CRT, chemoradiotherapy; RT, radiotherapy; RT-alt, altered fractionation radiotherapy; RT-hf, hyperfractionated radiotherapy; RT-std, standard radiotherapy.
radiotherapy interruptions were 3.8-fold more common and unplanned chemotherapy breaks were 3.4-fold more common among patients with ulcerative mucositis, and the frequency of radiation treatment breaks was higher with higher grades of ulcerative mucositis. Notably, the incidence of radiation treatment breaks resulting from ulcerative mucositis was greater in this study than in the clinical studies described in the systematic review. Patients with moderate or severe ulcerative mucositis, who comprised the majority of the study population, had 15.8% and 46.8% incidences of radiation treatment breaks resulting from ulcerative mucositis, respectively. This finding is consistent with the theory that radiation treatment breaks resulting from ulcerative mucositis are more common in clinical practice than they are within the controlled setting of clinical trials where there is more support for patients [4].

Although altered radiotherapy schedules and concomitant CRT may enhance the radiation treatment response, they are associated with greater rates of acute toxicity (see Tables 2 and 3). Paradoxically, if the toxicity of the altered radiation treatment or concurrent CRT becomes too great, it could result in more radiation treatment breaks because of ulcerative mucositis, which in turn would lead to worse outcomes and negate the benefits of the altered fractionation radiation treatment. Clearly there is a need for strategies that will reduce ulcerative mucositis and radiation treatment breaks to allow more effective therapies to be administered with minimal planned or unplanned interruptions.

**STRATEGIES TO REDUCE ULCERATIVE MUCOSITIS AND RADIATION TREATMENT BREAKS**

Various strategies have been developed to reduce ulcerative mucositis and the associated radiation treatment breaks. The molecularly targeted therapy cetuximab was recently approved by the U.S. Food and Drug Administration in combination with radiation for the de novo treatment of patients with locally advanced head and neck cancers as well as for patients with recurrent, platinum-refractory disease [54]. In a study of high-dose radiotherapy for head and neck cancer, the addition of cetuximab resulted in a lower rate of locoregional progression or death, a longer progression-free survival time, and a longer overall survival time without exacerbating common adverse events, including ulcerative mucositis [55]. Cetuximab has not been directly compared with cisplatin or other concurrent CRT regimens in a randomized trial, so it is unknown how local-systemic toxicity, survival, and locoregional tumor control rates compare between this newer approach and the standard of care with conventional chemotherapeutic agents.

An additional strategy to maintain tumor control without increasing the incidence of ulcerative mucositis is to calculate compensatory doses of radiotherapy for radiation treatment breaks using a linear quadratic model, with the goal of equalizing the biological effective dose between the initially planned and actually delivered radiation doses [10, 11, 56]. Using this model, it is possible to find a solution to recover from early interruptions, but because of the effects of accelerated repopulation, it is almost impossible to recover the dose loss from late radiation treatment breaks. Similarly, compensation after interruptions in altered fractionation is extremely difficult to achieve. Treatment prolongation has a negative impact on locoregional control and can be difficult to achieve in patients whose compliance might be strained by the symptoms associated with ongoing treatment.

As described above, the negative consequences typically associated with radiotherapy breaks were not observed in a series of trials that either administered radiotherapy 7 days/week without breaks [27, 28] or used intensive CRT with weekly breaks [49, 50]. Although this approach may preserve the efficacy of radiotherapy for head and neck cancer, it may also lead to greater morbidity.

One of the most commonly used strategies to avoid radiation treatment breaks is the prophylactic use of feeding tubes. Feeding tubes allow for continuous feeding even when patients are unable to swallow. This can help to prevent malnutrition and dehydration and some of their secondary effects. Even with feeding tubes, patients still require narcotic analgesics and topical remedies to treat pain. They can also suffer from local infections that can become systemic as a result of the breakdown of the mucosal barrier and associated immune system. The painful symptoms may respond to oral rinses or systemic opioid therapy; there is limited evidence that some agents (allopurinol mouthwash, GM-CSF, immunoglobulin, or human placental extract) may address the underlying mucositis effectively [57]. The ideal strategy would be to prevent the development of mucositis, thereby maintaining locoregional tumor control without resulting in greater radiotherapy toxicity. Few agents have been proven to be significantly effective in preventing mucositis in head and neck cancer [58]. Small studies suggest that local treatment with oral rinses such as 0.15% benzydamine [59, 60] or vitamin E [61] may prevent mucositis, but large, well-controlled studies of these interventions are sparse. A recent systematic review of the available evidence [58] concluded that a few interventions—including hydrolytic enzymes, ice chips, Chinese (herbal) medicine, and amifostine—may have some benefit in the prevention of mucositis. Patients receiving amifostine with concurrent CRT in a randomized, phase II trial had a significantly lower incidence of ulcerative...
mucositis \( p = 0.0001 \) [62], but subsequent results of two phase III trials did not show conclusive evidence of mucosal protection [63, 64]. The authors considered the doses used in the phase III trials to be potentially suboptimal, but the effectiveness of amifostine in the head and neck cancer setting remains questionable. Other radio-protective agents also have shown disappointing results in sufficiently powered randomized trials. For example, in a randomized trial of head and neck cancer patients [65], iseganan failed to produce a lower incidence of ulcerative mucositis or attenuate its clinical sequelae relative to placebo. A meta-analysis of randomized trials of ulcerative mucositis prophylaxis in irradiated head and neck cancer patients [66] showed that, overall, the use of various interventions reduced the odds of developing severe ulcerative mucositis (odds ratio, 0.64; 95% confidence interval, 0.46–0.88). However, when the outcome was assessed by patients rather than physicians, no significant difference was seen in outcome between the treatment and control groups.

Recently, i.v. administration of the recombinant human keratinocyte growth factor palifermin was shown to reduce the incidence of ulcerative mucositis in patients with hematologic cancers [67]. Its efficacy and safety have not been reported in patients with head and neck cancer; however, phase III trials are currently ongoing in locally advanced head and neck cancer in the U.S. and Europe and may provide evidence regarding the potential effectiveness of this agent in reducing acute CRT-induced mucositis.

Additional study is required to identify safe and effective strategies to prevent ulcerative mucositis, thereby preventing unplanned radiation treatment breaks.

**CONCLUSIONS**

Treatment intensification improves efficacy outcomes in head and neck cancer but can also lead to a higher incidence of acute adverse events such as ulcerative mucositis, often resulting in unplanned radiation treatment interruptions. For radiotherapy, the biological principle of accelerated repopulation of tumors during breaks has been broadly acknowledged, and the negative clinical consequences have been documented for unplanned radiation treatment breaks.

Alteration of radiotherapy schedules to reduce radiation treatment breaks—by administering radiotherapy 7 days/week to eliminate radiation treatment breaks to ensure constant tumor coverage—may also improve efficacy outcomes. However, these strategies may simultaneously increase the morbidity of radiotherapy, particularly ulcerative mucositis.

The ideal solution would reduce both ulcerative mucositis and unplanned radiation treatment breaks as well as the overall package time, but currently available strategies to achieve this goal have been proven to be inadequate, leaving a very important unmet medical need. Continued investigation of new therapies to attenuate ulcerative mucositis and other associated acute and chronic toxicities should result in the identification of strategies that reduce radiation treatment breaks, thereby improving both the tolerability and efficacy of radiotherapy in head and neck cancer. Awareness of the impact of mucositis and treatment breaks and additional prospective trials, like the RTOG 0435 trial, that evaluate new strategies for reducing mucositis are warranted in order to address these serious impediments to cure.

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