Int. J. Radiation Oncology Biol. Phys., Vol. 51, No. 3, pp. 571–578, 2001

0360-3016/01/$–see front matter

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PII S0360-3016(01)01690-X

CLINICAL INVESTIGATION **Head and Neck**

RANDOMIZED TRIAL ADDRESSING RISK FEATURES AND TIME FACTORS OF SURGERY PLUS RADIOTHERAPY IN ADVANCED HEAD-AND-NECK CANCER

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Purpose: **A multi-institutional, prospective, randomized trial was undertaken in patients with advanced head-and-neck squamous cell carcinoma to address (*1*) the validity of using pathologic risk features, established from a previous study, to determine the need for, and dose of, postoperative radiotherapy (PORT); (*2*) the impact of accelerating PORT using a concomitant boost schedule; and (*3*) the importance of the overall combined treatment duration on the treatment outcome.**

Methods and Materials: **Of 288 consecutive patients with advanced disease registered preoperatively, 213 fulfilled the trial criteria and went on to receive therapy predicated on a set of pathologic risk features: no PORT for the low-risk group ($n = 31$); 57.6 Gy during 6.5 weeks for the intermediate-risk group ($n = 31$); and, by random assignment, 63 Gy during 5 weeks ($n = 76$) or 7 weeks ($n = 75$) for the high-risk group. Patients were irradiated with standard techniques appropriate to the site of disease and likely areas of spread. The study end points were locoregional control (LRC), survival, and morbidity.**

Results: **Patients with low or intermediate risks had significantly higher LRC and survival rates than those with high-risk features ($p = 0.003$ and $p = 0.0001$, respectively), despite receiving no PORT or lower dose PORT, respectively. For high-risk patients, a trend toward higher LRC and survival rates was noted when PORT was delivered in 5 rather than 7 weeks. A prolonged interval between surgery and PORT in the 7-week schedule was associated with significantly lower LRC ($p = 0.03$) and survival ($p = 0.01$) rates. Consequently, the cumulative duration of combined therapy had a significant impact on the LRC ($p = 0.005$) and survival ($p = 0.03$) rates. A 2-week reduction in the PORT duration by using the concomitant boost technique did not increase the late treatment toxicity.**

Conclusions: **This Phase III trial established the power of risk assessment using pathologic features in determining the need for, and dose of, PORT in patients with advanced head-and-neck squamous cell cancer in a prospective, multi-institutional setting. It also revealed the impact of the overall treatment time in the combination of surgery and PORT on the outcome in high-risk patients and showed that PORT acceleration without a reduction in dose by a concomitant boost regimen did not increase the late complication rate. These findings emphasize the importance of coordinated interdisciplinary care in the delivery of combined surgery and RT.**

Head-and-neck cancer, Prognostic variables, Risk grouping, Postoperative radiotherapy, Overall treatment time.

INTRODUCTION

The overall treatment duration of radiotherapy (RT) has been recognized as a major outcome determinant of head-and-neck squamous cell carcinoma treated by RT alone (1). This is reflected in a reduced tumor control rate when the same dose is delivered over a longer time and by the need to deliver a higher dose to maintain tumor control proba-

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Supported by Grants CA-06294 and CA-16672 from the National Cancer Institute, Gilbert H. Fletcher Chair, and Texas Tobacco Settlement Funds.

Acknowledgments—We thank the faculty of the Departments of Head and Neck Surgery of the participating institutions for enrolling patients in this trial. We appreciate the help of Mary Jane Oswald and Lawrence B. Levy in the data analysis and Cathy Ramirez in manuscript preparation.

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Received Feb 7, 2001, and in revised form May 17, 2001. Accepted for publication May 19, 2001.

bility if the treatment duration is prolonged. The most plausible explanation for this phenomenon is that surviving clonogenic tumor cells undergo rapid repopulation in response to their depletion during the course of fractionated RT. This idea forms the rationale for attempting to improve tumor control by shortening the overall RT duration without reducing the dose. The results of Phase III trials addressing various accelerated RT regimens as primary therapy of head-and-neck cancers are consistent with this notion (2). Likewise, evidence has emerged to indicate that the overall time may also be important in determining the outcome of combined modality therapy. A number of retrospective analyses, for example, showed a trend toward an association between a >6-week delay in initiating postoperative RT (PORT) and worse locoregional control (LRC) and survival rates (3–5). Consequently, the current Phase III trial was undertaken to address the impact of the duration of PORT and the overall time of surgery plus PORT on the outcome of patients at high risk of relapse above the clavicle.

The risk assessment method of the present randomized study was based on the results of a previous Phase III trial conducted at the University of Texas M. D. Anderson Cancer Center (MDACC) designed to determine the optimal dose of conventionally fractionated PORT in patients with advanced head-and-neck carcinoma (6). That trial established the relative prognostic significance of various clinicopathologic features identified by several investigators from retrospective analyses. In brief, these included primary disease site, surgical margin status (7–9), perineural invasion (10), number and location of positive lymph nodes (11, 12), and presence of extracapsular extension (ECE) of nodal disease (12, 13). However, the study revealed no significant dose–response relationship for total doses ranging from 57.6 to 68.4 Gy. This apparent lack of a dose–response could, however, be explained by postulating that the beneficial effect on tumor control of doses >57.6 Gy was offset by tumor cell regeneration occurring during the additional time taken to deliver the higher doses (given at 1.8 Gy/d).

This follow-up randomized trial was designed to address three objectives. The first was to assess prospectively the validity of using clusters of clinicopathologic features in assigning therapy in a multi-institutional setting. The second was to test the hypothesis that microscopic tumor foci escaping surgical resection undergo rapid repopulation, and thus, shorten the duration of RT using a concomitant boost schedule would improve the outcome in high-risk patients treated with a combination of surgery and PORT. The third was to assess the impact of the total duration of the combined treatment on the outcome of high-risk patients.

METHODS AND MATERIALS

Patient and disease characteristics

Patients with histologic, proven squamous cell carcinoma of the oral cavity, oropharynx, larynx, and hypopharynx, who were deemed likely to require treatment with a combination of surgery and PORT, and having a Zubrod performance status of 0–2 were eligible for this trial. The 3 participating centers were the MDACC, University of South Florida H. Lee Moffitt Cancer Center and James A. Haley Veterans Hospital, and Mayo Clinic.

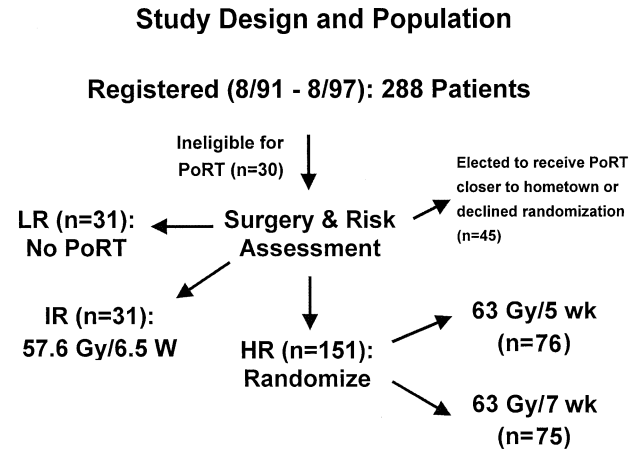


Fig. 1. Phase III trial design and patient allocation by risk grouping. LR = low-risk; IR = intermediate risk; and HR = high risk.

As illustrated in Fig. 1, the trial consisted of 2 components (i.e., registration for surgery and assignment for postoperative therapy). A total of 288 patients were registered and underwent surgical resection between August 1991 and March 1995. Thirty patients did not enter the second phase because of perioperative death ($n = 4$), major surgical complications ($n = 5$) or poor performance status ($n = 3$) precluding PORT, or the presence of gross residual disease ($n = 10$), synchronous tumors ($n = 5$), or other reasons ($n = 3$).

Of the 258 patients eligible for the second study component, 23 elected to receive RT elsewhere and 22 refused randomization predominantly for financial or logistic reasons (e.g., inability to find housing for therapy for ≤7 weeks or transportation to comply with the twice-daily regimen). Thus, the study population consisted of 213 patients (163 men and 50 women; median age 57 years, range 20–83); 185 were white, 14 Hispanic, 11 black, and 3 of other ethnic origins. The primary tumors were in the oral cavity in 80, oropharynx in 66, larynx in 38, and hypopharynx in 29 patients. The pathologic tumor stage was T3–4 in 129 (61%) and N2–3 in 123 (58%) patients. By American Joint Commission on Cancer grouping, 103 patients (48%) had Stage III and 81 (38%) Stage IV disease. Of the remaining patients, 9 had Stage II tumors and 20 had undergone nodal excision before referral, preventing proper assignment. ECE of nodal disease was present in 104 (49%), and direct extension of the primary tumor to the neck occurred in 14 patients (7%).

Interval between surgery and RT

Head and neck surgeons and radiation and dental oncologists evaluated patients before surgery, and, when necessary, teeth were extracted during surgery to prevent avoid-

able delay in starting PORT. The appointment for PORT was made as soon as the surgical wounds had healed sufficiently. Because a delay in starting PORT was found to be associated with a worse outcome (6), we considered it ethically unjustified to randomly vary the interval between surgery and RT.

The median interval between surgery and PORT was 31 days (range 18–91) for the entire group. It was 32 days (range 20–59) for the intermediate-risk group, 29 days (range 19–91) for the high-risk group receiving conventional fractionation (CF), and 31 days (range 18–91) for the high-risk group receiving accelerated fractionation (AF). The interval was >6 weeks in 20 patients. The reasons for the RT delay were slow wound healing in 6, fistula or bone exposure in 8, laryngeal edema or aspiration in 2, and poor compliance in 4.

Postoperative RT

Of the 213 patients, 31 had no adverse pathologic factors and were assigned to receive no additional therapy (no PORT). The other 182 patients received PORT, delivered in 1.8-Gy fractions, at the participating institutions (MDACC, $n = 107$; University of South Florida, $n = 58$; and Mayo Clinic, $n = 17$). The 31 patients with only 1 adverse factor other than ECE (intermediate-risk group) received conventionally fractionated RT to a dose of 57.6 Gy in 32 fractions during 6.5 weeks. Of the 151 patients with ECE or ≥2 factors (high-risk group), 75 were randomized to receive 63 Gy in 35 fractions during 7 weeks (CF) and 76 to receive the same dose and fraction number in 5 weeks (AF). The former group received 1 fraction/d, 5 fractions/wk for 7 weeks and the latter group, 1 fraction/d, 5 fractions/wk for 3 weeks and then 2 fractions/d (≥6-hour interfraction interval), 5 times weekly for 2 weeks.

Patients were treated with techniques appropriate to the site of disease and likely areas of spread, as reported earlier (14). The final dose was delivered to the tumor bed with ≥1.5-cm margin. Undissected areas treated electively received 54 Gy in 30 fractions, and dissected, pathologically negative, areas received a minimum of 57.6 Gy in 32 fractions, as in the previous trial. All intermediate-risk patients completed PORT, but 13 high-risk patients (5 in the 7-week arm and 8 in the 5-week arm) received <60 Gy because of disease progression ($n = 2$), death before completion ($n = 2$), acute side effects ($n = 1$), and lack of compliance ($n = 8$).

End points and follow-up

The study end points were LRC, survival, and morbidity. Patients were examined at least weekly during RT. After therapy completion, they were examined at 6-week intervals until the acute reactions subsided. Subsequent follow-up occurred at 3-month intervals the first year, 4-month intervals the second year, 6-month intervals the third year, and annually thereafter. LRC, survival rate, and late morbidity were calculated actuarially using the Kaplan–Meier method, and significance was assessed using the log–rank or chi-square test. All analyses were based on an intention to treat basis.

RESULTS

The length of follow-up in the 112 living patients was 22–83 months (median 59). At the last follow-up visit or death, 139 patients had no evidence of disease, 29 had recurrence above the clavicle (12 local, 16 regional, 1 combined), 27 had distant metastasis without locoregional relapse, and 18 had distant metastasis with local recurrence ($n = 3$) or regional relapse ($n = 10$), or both ($n = 5$).

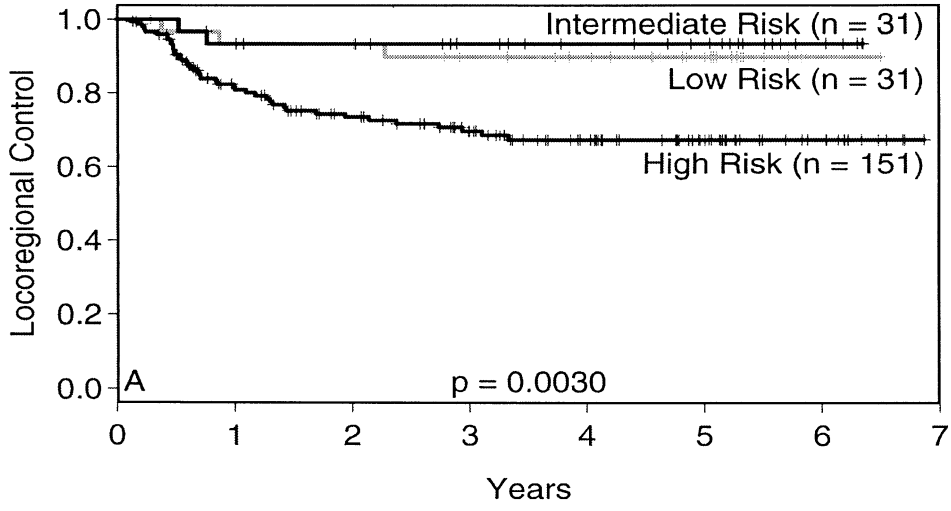
Figure 2A shows that the actuarial LRC rate of high-risk patients receiving 63 Gy was significantly lower than that of low-risk patients receiving no PORT and intermediate-risk patients receiving 57.6 Gy ($p = 0.003$). Figure 2B reveals a significant inverse relationship between the risk category and survival rate ($p = 0.0001$). The 5-year actuarial distant metastasis rate was 3%, 4%, and 33% for low-risk, intermediate-risk, and high-risk patients, respectively.

For high-risk patients, Fig. 3 reveals that AF yielded a trend for higher LRC ($p = 0.11$) and survival ($p = 0.08$) rates relative to CF. Figure 4 shows that the interval between surgery and PORT had a significant impact on the LRC and survival rates of patients receiving CF ($p = 0.02$ and 0.01, respectively) but not of those receiving AF ($p = 0.36$ and 0.50, respectively). The known pathologic adverse factors were equally distributed among these 2 patient groups (Table 1). Figure 5 demonstrates that the cumulative time of combined therapy significantly affected the LRC ($p = 0.005$) and survival ($p = 0.03$) rates. The distribution of risk features among the groups was not different.

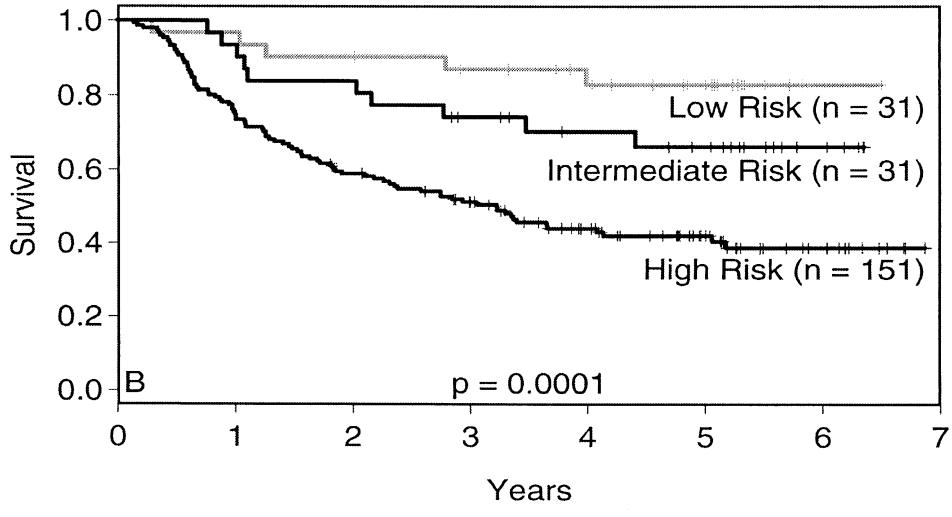
Table 2 shows the acute and late (i.e., manifesting for >3 months after RT completion) treatment morbidity, according to the Radiation Therapy Oncology Group/EORTC scoring system, in patients receiving PORT. The incidence of confluent mucositis induced by 57.6 Gy was significantly lower than that induced by 63 Gy given in daily 1.8-Gy fractions (16% vs. 36%, $p = 0.02$). In the high-risk group, AF induced an even higher incidence of confluent mucositis than did CF (62% vs. 36%, $p = 0.001$). The 2- and 5-year actuarial incidence of Grade 3–4 late morbidity was also significantly lower after 57.6 Gy than after 63 Gy ($p = 0.03$). However, no difference was found in the actuarial probability of a patient sustaining ≥1 late complications in the high-risk group receiving the two fractionation regimens ($p = 0.94$).

DISCUSSION

The present prospective randomized trial of combined surgery and PORT for advanced head-and-neck squamous cell carcinoma, designed on the basis of the findings of a previous Phase III study conducted at MDACC (6), produced a number of findings useful for refining the practice guidelines for combined surgery and RT for patients with the disease. First, it yielded a prospective validation that risk



(a)



(b)

Fig. 2. Actuarial (A) LRC and (B) survival curves by risk grouping.

assessment by clusters of surgical–pathologic features (i.e., oral cavity site, mucosal margin status, nerve invasion, >1 positive node, >1 positive nodal group, largest node >3 cm, ECE, and treatment delay of >6 weeks [7, 10, 12, 13, 15]) differentiates the need for, and dose of, PORT. The previous study (6) had been designed primarily to address the impact of moderate dose escalation on the LRC rate. An arbitrary scoring system, based on more equal weighting of the surgical–pathologic features, had been used to categorize patients into lower and higher risk groups. That trial did not demonstrate any improvement in LRC with RT dose escalation in either group. However, an analysis using the pooled data revealed the relative significance of various adverse features identified from retrospective analyses reported from many centers (i.e., ECE was the only significant independent variable and that combinations of ≥2 risk factors were associated with a progressively higher risk of recurrence). These findings formed the basis of the treatment assignments in the current prospective trial. The results showed that patients with no adverse surgical–pathologic features did not need PORT, because the 5-year actuarial LRC and survival rates achieved with surgery alone were 90% and 83%, respectively. Patients with 1 adverse feature other than ECE who received 57.6 Gy PORT had 5-year actuarial LRC and survival rates of 94% and 66%, respectively. This finding, consistent with our prior trial outcome, justifies the use of a moderate RT dose for patients having an intermediate risk of recurrence, particularly in view of the finding that 57.6 Gy induced a lower incidence of acute and late morbidity than did 63 Gy (Table 2). In contrast, high-risk patients (i.e., those with ECE or ≥2 other adverse features) had 5-year actuarial LRC and survival rates of 68% and 42%, respectively, despite having received a higher radiation dose (63 Gy). This result also confirms that the presence of ECE or clusters

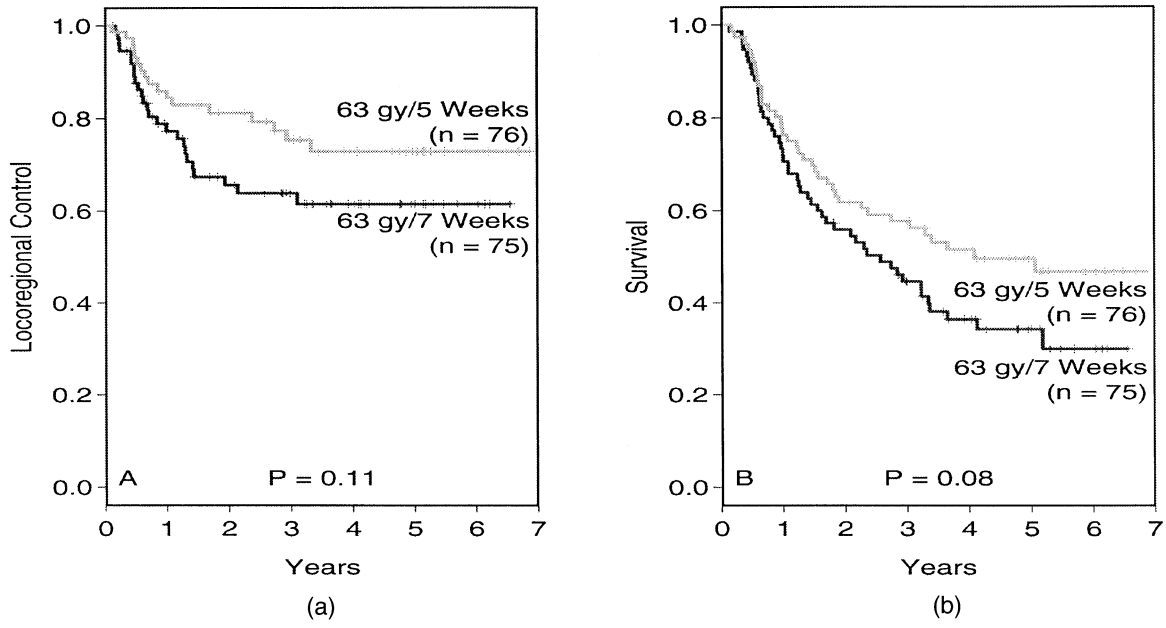


Fig. 3. Actuarial (A) LRC and (B) survival curves for high-risk patients as a function of the fractionation schedule of PORT.

of ≥2 other risk factors denotes a high risk of locoregional recurrence despite the administration of higher dose PORT.

Second, the current trial also established the impact of the overall treatment time on the therapeutic outcome for patients with high-risk features. The 5-year actuarial LRC rate for <11 weeks was 76% compared with 62% for 11–13 weeks, and 38% for >13 weeks ($p = 0.002$); the corresponding survival rates were 48%, 27%, and 25% ($p = 0.03$). The sample size was only sufficient to demonstrate a relatively strong trend toward a lower LRC rate with the use of a 7-week PORT schedule relative to a 5-week regimen. However, the findings that a >6-week interval between surgery and RT was detrimental in patients receiving the

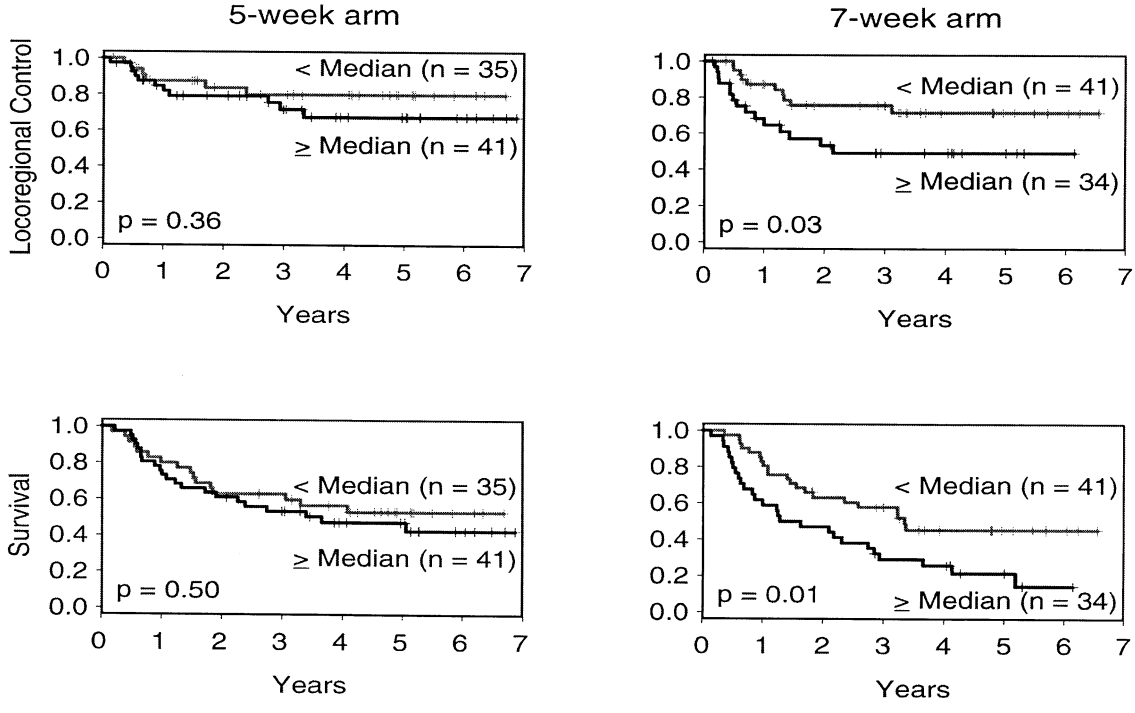


Fig. 4. Actuarial LRC and survival in high-risk patients as a function of the interval between surgery and the start of PORT.

Table 1. Distribution of individual adverse factors by treatment characteristics in the high-risk group

	Surgery–RT interval (wk)			RT duration (wk)	
Risk factor	≤4 (n = 65)	5–6 (n = 66)	>6 (n = 20)	5 (n = 76)	7 (n = 75)
ECE of nodal disease	53 (82)	52 (79)	12 (60)	61 (80)	56 (75)
>1 nodal group	40 (62)	46 (70)	12 (60)	46 (61)	52 (69)
≥2 positive nodes	45 (69)	48 (73)	16 (80)	56 (74)	53 (71)
>3-cm node	15 (23)	24 (36)	6 (30)	24 (32)	21 (28)
Oral cavity cancer	25 (38)	19 (29)	5 (25)	26 (34)	23 (31)
Microscopic + margin	7 (11)	12 (18)	2 (10)	11 (14)	10 (13)
Perineural invasion	19 (29)	14 (21)	3 (15)	17 (22)	19 (25)

Abbreviation: RT = radiotherapy; ECE = Extracapsular extension.
Numbers in parentheses are percentages.

7-week schedule and that completing the therapy in a cumulative time of >13 weeks yielded a highly significantly lower LRC rate advises against further randomization of patients with a prolonged delay in starting PORT. Thus, although the benefit of AF in the postoperative setting is not completely resolved, our data are consistent with the results of recent randomized trials showing that a number of AF regimens yielded better LRC rates in patients with unresect-

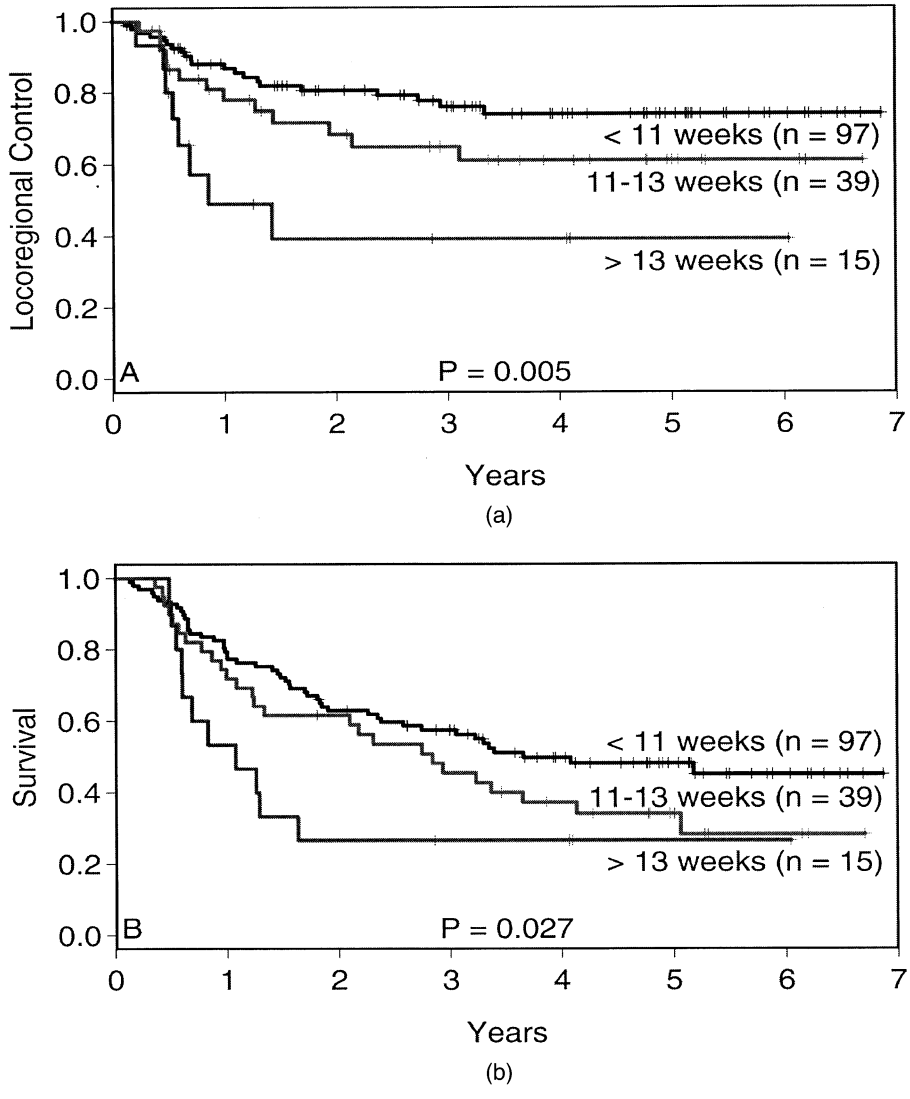


Fig. 5. Actuarial (A) LRC and (B) survival in high-risk patients as a function of the duration of the overall treatment "package" (i.e., from the day of surgery to PORT completion.

Table 2. Acute reactions and moderate–severe late treatment morbidity by radiotherapy dose and duration

	Intermediate risk	High risk	
Side effect	57.6 Gy/6.5 wk (n = 31)	63 Gy/5 wk (n = 76)	63 Gy/7 wk (n = 75)
Acute reactions (%)			
Confluent mucositis	5 (16)	47 (62)	27 (36)
Tube feeding*	12 (39)	39 (51)	35 (47)
Grade 3–4 late morbidity			
Ulcer/soft tissue necrosis	—	2	2
Fibrosis	1	19	13
Dysphagia	4	16	13
Fistula	—	2	5
Osteonecrosis requiring surgery	—	1	2
Chondritis	—	0	1
Total no. of complications	5	40	36
Patients with complications (n)	5	26	25
2-and 5-year actuarial rates (%)	17, 17	36, 38	36, 42

* The common practice is to prescribe tube feeding when needed.

able cancers receiving primary RT (1, 16). The current data also support the notion that microscopic tumor cell aggregates escaping surgical excision repopulate rather quickly before treatment completion. These findings emphasize that the combination of surgery and PORT should be considered a "treatment package" that needs to be delivered in a timely and coordinated fashion (17, 18). For example, when required, teeth should be extracted in conjunction with tumor surgery to prevent unnecessary delay in starting RT. It also underscores the significance of keeping the RT duration as short as possible to yield a better outcome. Protracted, split-course RT regimens are not justified, not even to avoid transient mucosal reactions, because the risk of recurrence is too high. We currently strive to complete the combined treatment in $<$11 weeks, which may require the use of an AF (e.g., concomitant boost) regimen or even initiating PORT before the surgical wound is completely healed.

Third, the results of this randomized trial demonstrated, for the first time, that AF by a concomitant boost regimen delivered in the postoperative setting does not increase the late complication rate. This finding is concordant with a large body of recent radiobiologic data showing that fraction size rather than RT duration is the major determinant of RT-induced injury to normal tissues manifesting as late complications (19).

Finally, the data show that locoregional recurrence still occurs in 24% of high-risk patients even when therapy is completed within 11 weeks, which may not be attainable in a fraction of patients because of delayed wound healing or logistic reasons. Thus, there is still room for improving the outcome in this subset of patients. One of the logical directions, being pursued in several centers, is to explore the role of combining chemotherapy or biologic response modifiers with RT in addition to surgery (i.e., trimodality therapy) in high-risk patients.

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