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CLINICAL INVESTIGATION **Skin**

RADIOTHERAPY FOR LOCALLY ADVANCED BASAL CELL AND SQUAMOUS CELL CARCINOMAS OF THE SKIN

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Purpose: To determine the outcomes of patients with locally advanced basal cell and squamous cell carcinomas of the skin treated with radiotherapy.

Methods and Materials: A retrospective review of the outcomes of patients with basal cell and squamous cell carcinomas treated with radical radiotherapy was conducted. Patients with T2 or more advanced disease or nodal disease were included. The clinical course after radiotherapy and factors that can affect locoregional control were analyzed.

Results: Four-year locoregional controls for basal cell and squamous cell carcinomas are 86% and 58%, respectively. The median time to recurrence of basal cell and squamous cell carcinomas are 40.5 months and 5.0 months, respectively. No deaths resulted from basal cell carcinomas, but 65% (30/46) of all patients with locoregional recurrent squamous cell cancers died from the disease. Uncontrolled locoregional disease was the cause of death in 81% (30/37) of all patients who died of squamous cell cancers.

Conclusions: Basal cell carcinomas can be well controlled with radiotherapy even when locally advanced. Squamous cell carcinomas have a much poorer outcome and can recur quickly after radiotherapy. Locoregional failure remains the predominant cause of death in recurrent squamous cell carcinomas. © **2004 Elsevier Inc.**

Advanced-stage skin cancer, Radiotherapy, Squamous cell carcinoma, Basal cell carcinoma.

INTRODUCTION

Basal cell and squamous cell carcinomas constitute the largest group of cutaneous epithelial cancers. For decades, radiotherapy has been used successfully to treat these cancers with excellent results. However, with advancement in surgical techniques, the population of patients with these cancers treated by radiotherapy has changed. Today, patients with basal cell and squamous cell carcinomas are often referred for radiotherapy only when the tumors are advanced and the patient is not a surgical candidate. The typical patient treated with radiation is an elderly individual with locally advanced disease or nodal disease. The results of radiotherapy in treating these patients are not well described in the literature. The purpose of this study is to examine the outcomes in patients treated with radiotherapy for locally advanced squamous and basal cell carcinomas in the province of British Columbia.

METHODS AND MATERIALS

Patients

The B.C. Cancer Agency (BCCA) is the only institution providing radiotherapy services in the Canadian province of British Columbia (population 4.5 million). A retrospective review of all patients treated with radical radiotherapy for squamous cell carcinoma or basal cell carcinoma from 1994 to 1998 in the BCCA was undertaken. Patients had histologically proven disease and must have had locally advanced disease by satisfying one of the following criteria: (*1*) T2 or above (tumor size > 2 cm or deeply invasive disease) by International Union Against Cancer (UICC) 1997 TNM staging (1), or (*2*) node-positive disease by clinical or radiologic examination.

A total of 182 patients satisfied the criteria. Sixty-one had basal cell carcinoma and 121 had squamous cell carcinoma. Patients were referred either after a biopsy alone or after the tumor had recurred despite a previous attempt at curative resection. Both groups were included in the analysis. Referrals were based on patient and physician preference. The group treated with primary radiotherapy often included patients who were very elderly, and larger tumors that would have required major reconstuctive work if treated with primary surgery. The median age of the current cohort is 78 years (range, 31–103 years). Median follow-up of patients who are alive was 42 months (range, 1.4–97.1 months). The male:

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Table 1. Tumor and patient characteristics by histology

	Basal cell carcinoma	Squamous cell carcinoma
T stage		
T1	0%	6%
T2	13%	19%
T3	61%	41%
T4	23%	12%
T_x	3%	22%
Node-positive	0%	31%
Location		
Head and neck	100%	84%
Trunk	0%	9%
Extremities	0%	7%
Presentation		
Primary treatment	49%	45%
Recurrent disease	51%	55%

female ratio is 2.3:1. Table 1 shows the tumor characteristics of the population in this report.

Treatment

Radiotherapy was delivered with orthovoltage X-rays alone, electrons alone, megavoltage photons (cobalt, 4-MV or higher energy), or a combination of various electrons and photons. In general, orthovoltage X-rays or electrons were used alone when the target volume was the primary tumor plus margin, and megavoltage photons were used when deeper dose penetration was required such as in regional nodal irradiation or in treatment of a deeply invasive primary tumor. A number of dose-fractionations were used. The most common were 3500 cGy in 5 fractions, 4000–4500 cGy in 10 fractions, 5000–5500 cGy in 15–20 fractions, 6000 cGy in 25 fractions, and 6000–7000 cGy in doses of 200 cGy per fraction. Both the dose-fractionation scheme and target volume were entirely at the discretion of the treating radiation oncologist. When the primary tumor alone was radiated, the field was outlined such that the tumor and microscopic disease were included in the 90–95% isodose line. Table 2 shows the treatment characteristics of patients in this report.

Follow-up

Patients were seen weekly during their radiotherapy and 6–8 weeks after completion of radiotherapy. After the first postradiotherapy clinic visit, patients were followed every 3–6 months at the discretion of their radiation oncologists. Locoregional failure is defined as any recurrent disease either at the primary site or first echelon lymph nodes. Because many patients were elderly, sometimes no formal clinic visits were arranged after their first postradiation follow-up appointment. These patients were often followed primarily by their family physicians. The authors took additional steps in establishing the treatment outcomes when the retrospective chart review was done. The primary care physicians and sometimes the patients themselves were contacted for additional information on the clinical course of the patient. In instances where the patient had expired, the tumor registry or primary care physician was contacted to ascertain the cause of death. Because the B.C. Cancer Registry is administered by the B.C. Cancer Agency, data on deaths and causes of death are reliable. The authors have also checked the history of the patient when the causes of death were assigned.

Analyses

The overall survival, disease-specific survival, and locoregional failure rates of the patients were calculated from the start of radiotherapy. Because no basal cell carcinoma patient died from their disease, and because the vast majority of patients who died from squamous cell carcinoma had a locoregional recurrence, locoregional control was used as the primary endpoint when analyses were done for factors affecting disease control. Kaplan-Meier curves were generated for factors that can affect locoregional control, and log–rank statistics were used in the univariate analyses. Because widely different dose-fractionations were used for treating this patient population, dose was analyzed as a categorical variable by dividing into four groups (<4000 cGy, 4000–4900 cGy, 5000–5900 cGy, and ≥6000 cGy) as shown in Table 2. Cox regression was done for multivariate analysis entering into the model those factors with a p value ≤0.2 in univariate analyses.

RESULTS

Survival

There were no deaths attributable to basal cell carcinoma. Thirty-seven of the 121 patients with squamous cell carcinoma died of their cancer. The Kaplan-Meier estimate of disease-specific survival at 4 years for squamous cell carcinoma is 60% (Fig. 1). The population is very elderly, and deaths from other causes far outweigh deaths from cancer. The Kaplan-Meier estimates of overall survival at 4 years

Table 2. Treatment characteristics

Total dose*	<4000 cGy	4000–4900 cGy	5000–5900 cGy	≥6000 cGy
Basal cell cancer	16%	25%	49%	10%
Squamous cell cancer	13%	18%	47%	22%

* Commonest dose fractionation in each group = 3500 cGy in 5 fractions, 4500 cGy in 10 fractions, 5000 cGy in 15–20 fractions, and 6000 cGy in 25 fractions.

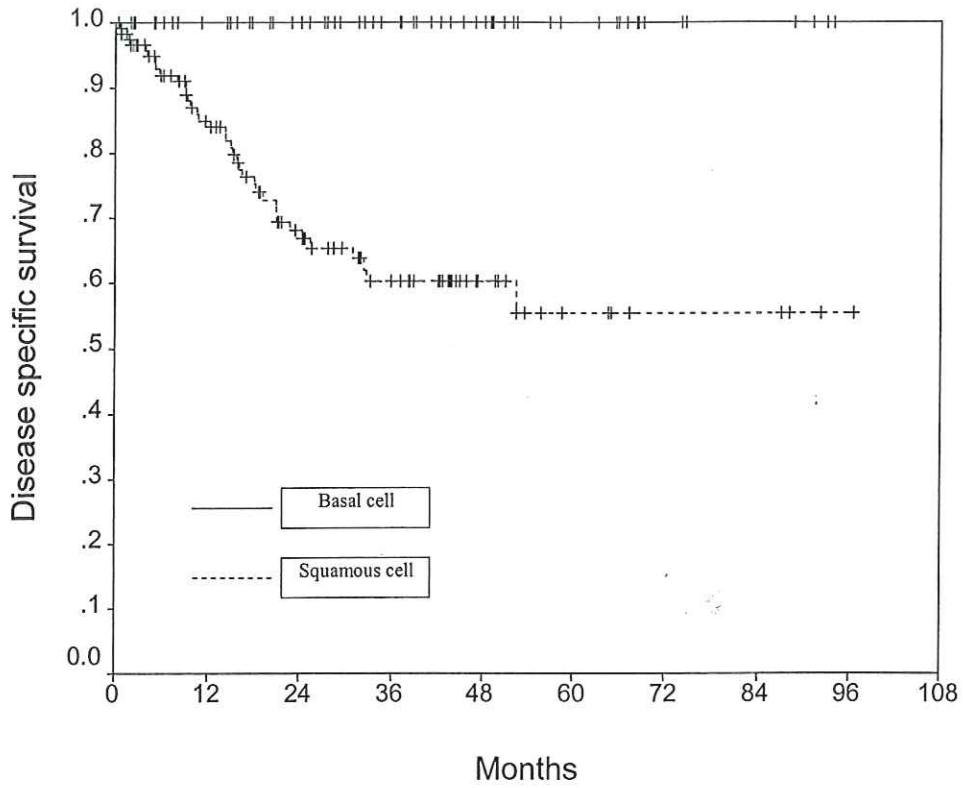

Fig. 1. Kaplan-Meier estimates of disease-specific survival of patients with basal cell and squamous cell carcinomas.

for patients with basal cell carcinomas and squamous cell carcinomas are 76% and 27%, respectively.

Locoregional control

Kaplan-Maier estimates at 4 years of locoregional controls for basal cell carcinoma and squamous cell carcinoma are 86% and 58%, respectively (Fig. 2). Univariate analyses were done using log–rank statistics to identify factors that can affect locoregional control. The results are shown in Table 3.

For squamous cell carcinomas, patients had a poorer locoregional control when they were treated with radiation for recurrent disease compared to when they were treated at their primary presentation with radiotherapy. Type of radiation beam was also significant in the locoregional control of squamous cell cancer, yielding a p value of 0.01 in the log–rank test. However, this difference mainly applies when one compares patients treated with mixed beams to patients treated with either photons or electrons. Patients treated with photons alone or electrons alone have similar outcomes. Multivariate analysis was done using Cox regression with factors having a p value ≤ 0.2 in univariate analyses (type of radiation beam, primary presentation vs. recurrent disease and nodal status). Type of radiation beam and whether radiation was given as primary treatment or recurrent disease remained significant with p values of 0.04 and 0.05, respectively.

For basal cell carcinomas, none of the seven disease factors or treatment factors was found to be significant in affecting locoregional control on univariate or multivariate analysis.

Patterns of recurrence

Eight patients with basal cell carcinomas recurred. They recurred a median of 40.5 months after radiotherapy (range, 19–89 months). All recurred with local disease without nodal metastases. None developed distant metastases. Four had successful excision of the recurrence, and two had a repeat course of radiotherapy. One patient was incumbent in an extended care facility with a slowly growing tumor, and the final patient refused retreatment at last follow-up.

Locoregional recurrence developed in 46 of 121 patients with squamous cell carcinomas. They recurred a median of 5 months after radiotherapy (range, 0.3–48 months). In all but 5 patients locoregional recurrence occurred within 1 year, and all but 1 patient recurred within 18 months. 65% (30 patients) of the 46 patients who had a locoregional recurrence died of their cancer. Therefore, of the 37 patients with squamous cell carcinomas who died of their cancer, 30 had a locoregional recurrence and only 7 (7/37 or 19%) died of distant metastases without failing locally first.

Prophylactic regional nodal radiation in squamous cell carcinoma

To examine the effects of prophylactic nodal radiation, patients who were treated with radiotherapy on primary presentation were analyzed so that the effects of a surgical neck dissection do not influence the results of analysis (Fig.

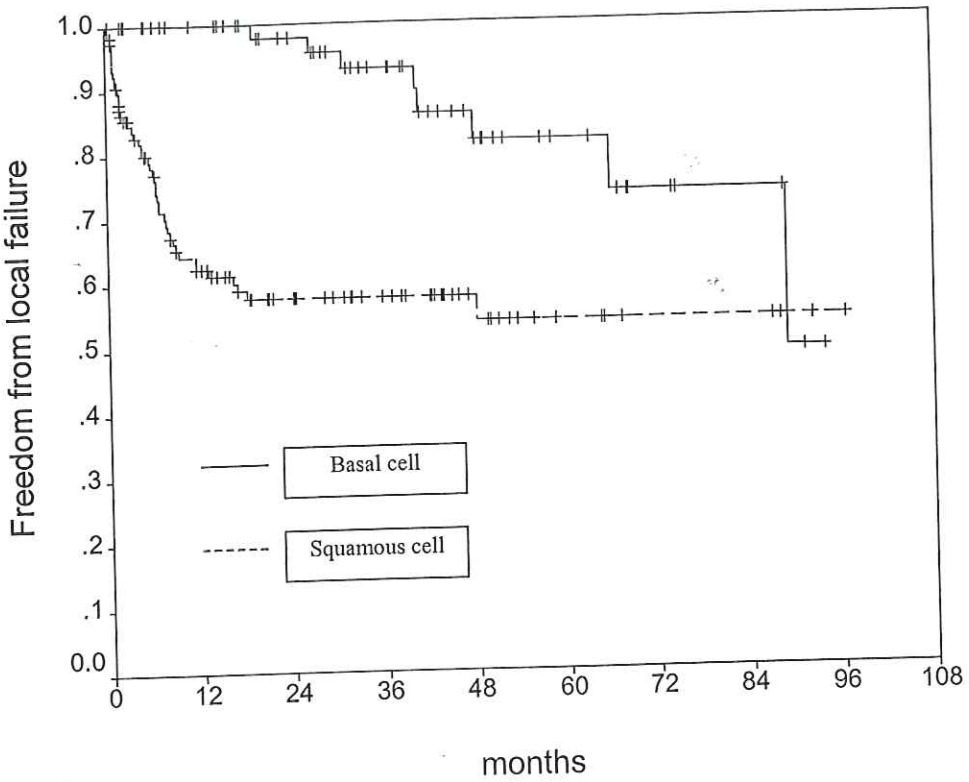

Fig. 2. Kaplan-Meier estimates of freedom from local failure in patients with basal cell and squamous cell carcinomas.

3). Among 42 squamous cell carcinoma patients who presented with no clinical nodal disease and were treated with radiotherapy on primary presentation, 37 had treatment to the primary site without coverage of the nodes. Locoregional failure occurred in 11 patients (30%). Five patients had radiation with the field including the draining nodes, and locoregional failure occurred in 1 patient (20%). The crude locoregional failure rates of the 37 patients with T2, T3, or T4 disease presenting without nodal involvement and not given prophylactic radiation were 14% (1/7), 29% (7/24), and 50% (3/6), respectively.

Table 3. Significance of disease and treatment factors on locoregional control, *p* values of log–rank test in univariate analysis are shown

	Basal cell carcinoma	Squamous cell carcinoma
Nodal status	Not defined	0.20
T stage	0.72	0.24
Primary presentation vs. recurrent disease	0.45	0.04
Location of tumor	0.78	0.70
Photons vs. electrons vs. mixed photons/electrons	0.14	0.01
Target volume (tumor only vs. tumor and nodes)	0.45	0.60
Dose	0.15	0.54

DISCUSSION

The current publication is the largest series on patients treated with radiotherapy for more advanced epithelial skin cancers and provides valuable information on the outcomes of such patients who are more and more commonly seen in a modern day radiotherapy practice. Our series shows that basal cell carcinomas and squamous cell carcinomas have different clinical behaviors. Basal cell carcinomas recur late (median, 40 months in this report), do not spread to regional nodes even upon recurrence, and are rarely fatal even if treatment fails. Squamous cell carcinomas recur early (median 5 months in our series), have a higher locoregional failure rate, and are the cause of death in two-thirds of patients when radiotherapy fails. This difference in clinical course based on histology agrees with the clinical impression of the authors, but interestingly is not well described in the literature. Of the few published series in the last 20 years, the studies by Mendenhall *et al.* (2) and Lee *et al.* (3), both from the University of Florida College of Medicine at Gainesville, deal with subjects similar to the current series. Mendenhall reported on T2–T4 carcinoma of the skin of the head and neck, and Lee reported on T4 carcinoma of the skin of the head and neck. Histology was not found to be important in local control in the Gainesville series, but detailed analysis was not presented. The number of patients in both reports is smaller than the current series (99 and 67, respectively), and the difference might not be apparent to

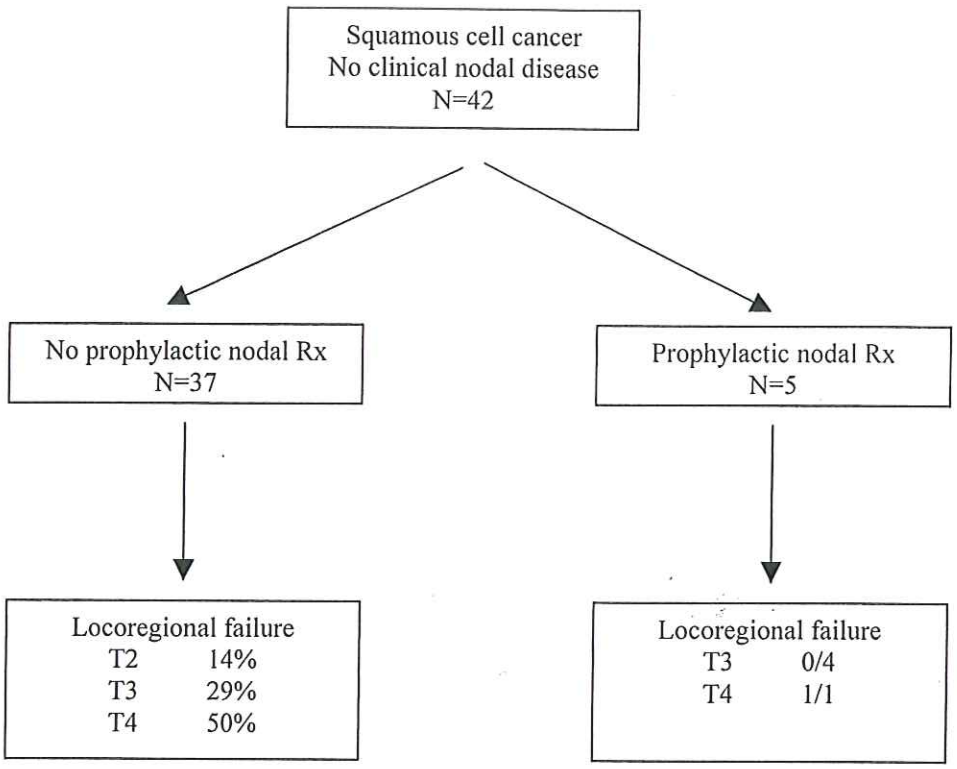

Fig. 3. Outcomes of squamous cell carcinomas, presented for primary treatment with no clinical nodal disease, treated to the primary alone.

these authors because analyses were done mainly by pooling both histologies together. The experience at the Mallinckrodt Institute of Radiology was reported by Lovett *et al.* (4) in 1990, and later expanded and reported by Locke *et al.* (5). The Mallinckrodt reports contained epithelial skin cancers of all histologies and stages. With larger numbers, squamous cell carcinomas were found to have a significantly worse local control than basal cell carcinomas by these investigators.

Although there were no deaths attributable to basal cell carcinomas, the 4-year disease-specific survival for locally advanced squamous cell carcinomas was only 60%. The current report illustrates the importance of achieving locoregional control. Eighty-one percent (30/37) of all deaths from squamous cell cancers had locoregional recurrences first. In younger and medically fit patients, a combined surgical and radiotherapeutical approach can be adopted to improve on locoregional control. However, with the advanced age of patients typical in this population, more intensive treatment to maximize locoregional control is often poorly tolerated. In our multivariate analysis, patients treated for recurrent cancers have poorer locoregional control. This is also found to be the case in numerous reports (2–6). Unfortunately, this is not a modifiable factor. In the earlier publication of the Mallinckrodt series, (4) Lovett *et al.* found that patients treated with electrons have a poorer outcome. Silva and colleagues from the Princess Margaret Hospital also had similar findings (7). Yet, the later update of the Mallinckrodt series by Locke *et al.* (5) did not show that electron beam therapy gives a worse outcome. Our series shows that patients treated with electron beams alone have a similar control rate compared to patients treated with orthovoltage beams, but patients treated with a mixed photon–electron beam have a distinctly worse locoregional control. This is most likely the result of patient selection because a mixed beam is used to treat deeper tumors or tumors with known nodal disease. The technique of prescribing an electron beam may also have contributed to the poorer outcomes reported initially by Lovett and also by Silva.

Improving on the radiotherapy volume may help in the locoregional control of patients with squamous cell carcinomas. Due to the retrospective nature of this report, we are not able to distinguish between local failure and regional failure. However, patients with locally advanced squamous cell carcinomas (particularly T3 and T4 patients) are found to have a significant locoregional failure rate (29% and 50%, respectively) (Fig. 3) when prophylactic nodal radiation is not given. Nodal recurrence rates based on whether prophylactic nodal radiation is given are only given in the relatively old publication by Mendenhall *et al.* (2) They mentioned that of patients with previously untreated T2–T4 disease with clinically negative necks, there were no neck recurrences whether elective neck irradiation was employed or not. Among patients treated with radiotherapy for T3–T4 recurrent squamous cell carcinomas, 2/7 patients developed neck disease without elective neck irradiation and 2/10 patients developed neck disease with elective neck irradia-

tion. Despite the uncertainty, the issue of whether elective neck irradiation should be given may only have academic interest. Practical limitations in this elderly population dictate clinical practice: decision on elective nodal radiotherapy obviously depends on the location of the primary and the general condition of the patient. From our series, it seems reasonable to include the first echelon nodes in the radiation volume for T3/T4 disease when it is practically feasible.

Another strategy for improving on the locoregional control is by giving a higher dose of radiation. Our series shows no significant difference in the locoregional control achieved by different dose fractionations. Unfortunately this issue remains unclear after one examines the available literature to date. The two Gainesville series (2, 3) did not analyze for dose response. The Mallinckrodt series (4, 5) showed that patients did better when given a higher dose per fraction. This is almost certainly a result of the preponderance of smaller lesions treated with a higher dose per fraction. Of the two series on epithelial skin cancers from the Princess Margaret Hospital, Silva *et al.* (7) found that total dose was statistically significantly associated with local failure, but the relationship was not inversely proportional. Tsao *et al.* (8) found no difference when the control rate was analyzed for dose, probably because this latter series includes mainly small lesions with excellent control after radiotherapy. However, given the relatively small volume of radiation to the gross disease required in treating these patients, a practical strategy in treating patients with bulky local disease is to increase the total dose delivered to the gross disease beyond what is traditionally prescribed. For example, in British Columbia, 6000 cGy in 25 fractions is often given to this group of patients. Consideration can be given to deliver an additional 1000 cGy in 200-cGy fractions to the gross bulky disease. The higher dose is often well tolerated because the volume is relatively small.

CONCLUSIONS

Basal cell carcinomas can be well controlled with radiotherapy even when locally advanced. Squamous cell carcinomas have a much poorer outcome and can recur quickly after radiotherapy. Locoregional failure remains the predominant cause of death in recurrent squamous cell carcinomas of the skin, and future efforts should be directed to improve the locoregional control rate in this group of patients.

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