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CLINICAL INVESTIGATION **Head and Neck**

THE BENEFITS AND PITFALLS OF IPSILATERAL RADIOTHERAPY IN CARCINOMA OF THE TONSILLAR REGION

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Purpose: Ipsilateral techniques designed to restrict treatment to the primary tumor and neck on the same side have been used in selected cases of cases of carcinoma of the tonsillar region at our institution for many years. The primary purpose of this study is to evaluate the risk of failure in the opposite neck in cases selected for unilateral radiotherapy over a 21-year period.
Methods and Materials: Ipsilateral radiotherapy techniques were used in 228 of 642 patients with carcinoma of the tonsillar region from 1970 to 1991. Local control, regional lymph-node control (including contralateral failure), and survival were calculated for different degrees of tumor extent treated with these techniques.
Results: Mean follow-up was 7 years. Cases tended to be T1 and T2, with N0 disease. The 3-year actuarial local control rate was 77% and cause-specific survival was 76%. Opposite neck failure was seen in 8 patients (crude rate of 3.5%). In the earlier period of the study, primary coverage was problematic in a proportion of cases and resulted in higher rates of local failure.
Conclusion: Appropriately selected cases of carcinoma of the tonsil show minimal risk of failure in the opposite neck with ipsilateral techniques. Patients should undergo computed tomography planning to ensure adequate target coverage.

Tonsillar carcinoma, Lymph nodes, Radiation therapy, Contralateral failure.

INTRODUCTION

Permanent xerostomia is a frequent complication afflicting patients undergoing radiotherapy for head-and-neck cancer. It arises chiefly from a direct effect of radiotherapy on the major serous-secreting salivary glands. Usually permanent and severe, it frequently compromises nutrition and significantly enhances and accelerates dental decay. There is no satisfactory treatment for this adverse long-term outcome in the cured head-and-neck patient who is affected.

Carcinoma of the tonsillar region shows a high success rate following radiotherapy (1). It is also a lateralized tumor, at least in its early phase of presentation. Murthy and Hendrickson questioned the need to treat the opposite neck in an effort to spare morbidity, and provided support for this approach in a small series (2). However, Lusinchi *et al.* opposed this approach, commenting that contralateral palpable lymph nodes may be found with well-lateralized tumors; this view appears to represent the prevailing opinion in many centers (3). Recently, reports again support the suggestion that many patients can be appropriately treated with ipsilateral radiotherapy techniques (4, 5).

At the Princess Margaret Hospital (PMH), the radiotherapy practice has been to employ an ipsilateral technique in early-stage and selected higher-stage presentations of carcinoma of the tonsillar region; this experience is presented to address this controversy. From the outset, the primary purpose and question of this study was to assess the incidence of regional lymph-node failure in the contralateral neck in patients using radiotherapy techniques intended to minimize treatment to contralateral parotid gland through its exclusion from the high-dose target volume.

As secondary questions, we also wanted to examine control at the primary site and the complication rates using these techniques, because "geographic miss" has been described with techniques not employing, or only partially using, parallel-opposing portals (6). This was, in large part, related to underdosage of lateralized lesions in wedge-pair techniques, where the beams converge obliquely and may cut across a anteriorly or posteriorly located tumor, and

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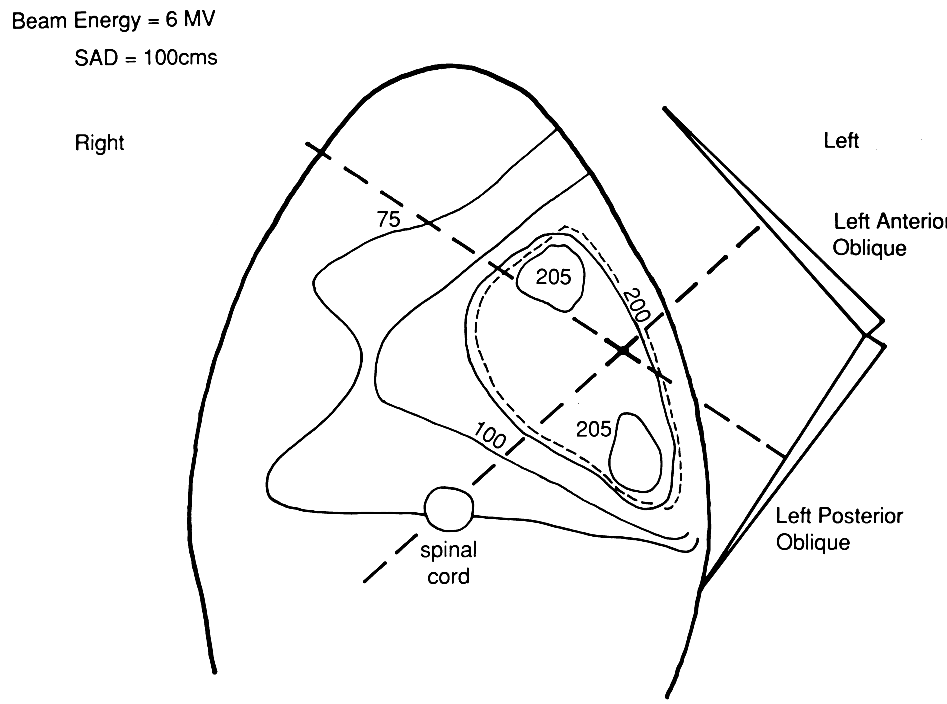

Fig. 1. Typical distribution of a plan used for a unilateral treatment with an oblique wedge-pair field arrangement. This example is for 6-MV photons, although the majority of cases in the study were treated with cobalt. For the planning technique used, the patient contour was available and the position of the spinal cord was identified; however, other anatomic structures were not present to guide the radiation oncologist in drawing the high-dose target (dotted lines). Reliance on coordinates shared between a lateral radiograph and the initial paper contour was used to guide the position of relevant anatomy and the location of the tumor (see "Methods"). The spinal cord receives approximately 30% of the dose prescribed to the target for the beam arrangement shown. The 100% isodose is normalized to the TAD, which for this case, is the 200% point.

because of tapering of the radiotherapy distribution, which may underdose at the most medial point of tumor. It was also related to constriction of electron-beam isodose curves, when these were used in the ipsilateral plans (6). Wang has also suggested that the use of ipsilateral radiotherapy techniques alone, especially the ipsilateral oblique-wedge pair, may not be optimal because they may result in unnecessary radiotherapy morbidity (7). The particular concern is the potential damage to mandibular and/or temporal bone, or spinal cord due to the higher-dose areas usually found at the entrance of the portals, as compared to the central region of the distribution (7) (Fig. 1).

Finally, we wanted to provide suggestions, based on our experience, concerning case selection for unilateral radiotherapy of tonsillar carcinoma and principles to follow for the technical delivery of these techniques. While primarily a descriptive paper, this report illustrates some of the benefits and pitfalls of this approach. The evolution of our treatment policies over two decades provides some unique data that is especially applicable to the contemporary era of three-dimensional (3D) treatment planning.

METHODS AND MATERIALS

Patients were included if they received curative exclusive ipsilateral radiotherapy between January 1970 and December 1991 at Princess Margaret Hospital (PMH) at their first presentation with carcinoma of the tonsillar region, and did not have a prior or concurrent malignancy, other than treated superficial nonmelanomatous skin cancer or *in situ* carcinoma of the uterine cervix. Patients managed with surgery were not included (16 patients in 21 years). The decision to use an ipsilateral technique was largely based on physician preference over the period of the study, and the proportion receiving this treatment increased in the later years of the study (see "Results"). Generally, the principle was to use ipsilateral radiotherapy to minimize dose to the contralateral parotid tissue to reduce the incidence of symptomatic xerostomia. In some instances, it was apparent that the technique was used to maximally spare mucosal tissue from the irradiation volume, generally in elderly or debilitated patients, to lessen acute morbidity or minimize chronic irradiation-induced loss of taste. In certain instances, the treatment comprised moderate-dose megavoltage external-beam radiotherapy combined with an interstitial implant or an intraoral cone to achieve the goals of mucosal sparing. No attempt was made to separate these goals retrospectively, because they were not explicitly described in the medical record over the time period of the study. Consequently, no cases treated with ipsilateral radiotherapy are excluded, even though they may have been intentionally treated with unusually small volumes at the primary site to minimize mucosal-based toxicities. All cases were followed for the duration of the study in the multidisciplinary head-and-neck clinics of PMH.

Clinical classification and definitions

The criterion for designating a technique ipsilateral was that the opposite neck should have received a dose less than 35 Gy in any portion of the contralateral neck volume. This dose was chosen to reflect traditional practice at PMH, where a 2.5-Gy daily-fractionation course to 35 Gy was considered the lower limit of dose to sterilize microscopic disease. In fact, the doses to the contralateral neck volume were observed to be much lower than this.

The contralateral neck volume is defined in this study as the volume extending from the maximum contralateral facial contour to a sagittal vertical plane located 4 cm medially. This 4-cm margin was derived by assessing the location of involved lymph nodes and the parotid glands in a sample of six contemporary N-positive cases staged with computed tomography (CT) scans. Because the medial extent of the contralateral neck volume extends inferiorly into the neck, and superiorly into the face, it encompasses both the contralateral regional lymph nodes and the contralateral parotid gland. For this patient series, this was appropriate because the majority of patients were treated with customized 3D compensators, and the external contour of the face and neck at the point of beam entry constituted a flat vertical surface from the stand-point of dosimetry. Thus, tapering of the neck below the mandibular region was not an issue nor did patients receive "cone-down" boosts to any areas, which could perturb the "rectangular" character of the dose distributions deep inside the patient's anatomy. The dosimetric features and nominal prescription dose for each case provided the ability to calculate target absorbed dose (TAD) and maximum dose according to the International Commission on Radiation Units (ICRU) (8). In addition, the minimum dose in the planning target volume was also calculated from the distributions. Also, maximum, minimum, and mean doses in the contralateral neck volume were obtained. Notably, the specific location of the contralateral parotid could not be identified on a case-by-case basis because these were not planned with CT (see below). Consequently, the position of the gland in the anteroposterior direction could not be verified reliably. Although we have regarded the dose calculated to the contralateral neck volume to be similarly distributed to the opposite parotid gland, these calculations may be an overestimate. This is because, in an ipsilateral wedge pair, the usual technique in the study, any dose to the contralateral neck was more likely to be distributed to the opposite anterior neck level-2 region and less likely to be in the posteriorly-located contralateral parotid (Fig. 1).

Patients were staged retrospectively using the 1992 TNM (identical to the 1997 TNM for oropharynx cancers) classification of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC). All were staged clinically using the same methods. Cross-sectional imaging with CT or magnetic resonance imaging (MRI) were not employed for stage allocation purposes and were only available in some of the most recent cases. Among other features, prospectively-documented information also included maximum lymph-node dimensions and node fixation, involvement of tongue base, palate, tonsillar pillars, posterior pharyngeal wall, glossotonsillar sulcus, and the soft palate/uvula region.

The degree of involvement of the base of tongue and soft palate were also categorized as follows (Fig. 2): lesions involving 1 cm or less of the lateral ipsilateral hemistructure of the soft palate or tongue base were classified as having

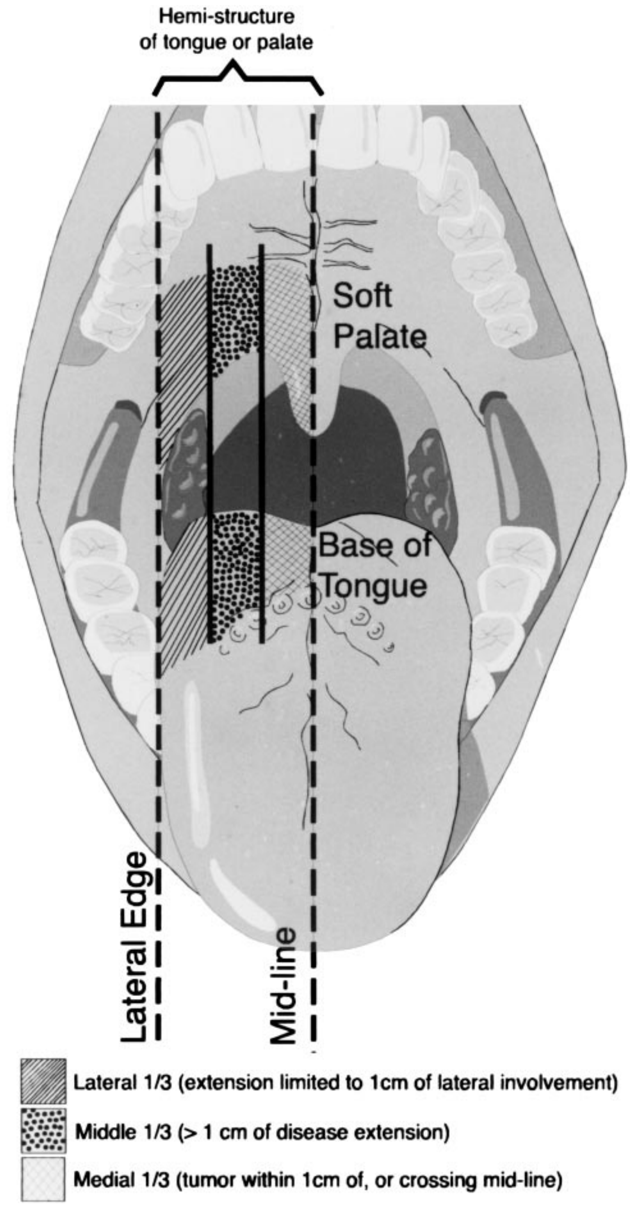

Fig. 2. Schematic illustration of the region of the soft palate and base of tongue to indicate classification of disease extension from the tonsillar region toward the midline. When classifying cases, specific statements in the medical records were used without further judgment. In this process, lateral "hemistructure" involvement was classified when either 1 cm of lateralized involvement was described or in any case where involvement was present but the degree of involvement was not stated explicitly.

lateral hemistructure involvement. Lesions extending to within 1 cm of the midline, or crossing the midline were classified as involving the medial hemistructure. The remaining intermediate extension lesions were classified as involving the middle hemistructure of the soft palate or tongue base. Lesions in which tongue base and/or palate involvement was documented to be present but where the actual extent was unstated were "down-staged" to lateral involvement to avoid "stage creep."

Radiotherapy technique and target coverage

The two-field wedged-pair technique was the standard technique, intended to encompass the primary tumor and the ipsilateral level-2 lymph-node region in all cases (Fig. 1). Additional treatment of lymph-node levels 3 and 4 on the ipsilateral side used a separate junctioned anterior lower neck field to the appropriate hemi-neck.

CT planning was not used during this time period. Treatment was planned using three contours through the head-and-neck region of interest, including the midpoint of the tonsillar region. These contours were taken from a semirigid plastic customized immobilization mask and transcribed to a standard life-sized paper format using a contour taker. The contours contained identifying coordinates, referenced back to a lateral radiograph of the patient wearing the mask. No identifying anatomy was evident, other than the location of the spinal cord (obtained from the lateral radiograph and transposed to the center of the contour), and the external contour of the face and neck. A high-dose volume was outlined on a single contour by the radiation oncologist and became the basis for plan development. The mask was also used to provide a physical template for manufacture of unique metal alloy missing-tissue-dose compensators for each patient.

Plans used detailed isodose distributions taking full 3D compensation to the maximum point of the contour at the point of beam entry, and the printouts for the plan were maintained in the radiotherapy record. They contained details about wedge angles, hinge angle, field sizes, and energy. They also showed the life-sized external patient contour, spinal cord position, and the radiation dosimetry with the intended high-dose target volume corresponding to the "single slice" volume outline provided by the radiation oncologist on the original paper contour (Fig. 1). The radiation oncologist chose the point of prescription, usually corresponding to an appropriate isodose on the periphery of the target volume. After 1987, all prescriptions corresponded to the TAD central axis dose point specified by the ICRU (8).

While a two-field wedge-pair was most commonly used, the same planning principles were used for planning alternative techniques, including ipsilateral electrons, mixed-beam electrons and photons, and weighted photon-beam plans.

All plans were evaluated by two individuals (B. G. and B. O'S.). The evaluation focused on a critical evaluation of radiotherapy dose coverage of the tumor in the cross-sectional plane, using the known information about tumor location and extent for each case. The superior and inferior coverage of disease was not assessed and was assumed to be satisfactory, as this component of planning was based on definable radiographic skeletal landmarks. However, cross-sectional planning was considered at greater risk (6, 9). Consequently, a life-sized transparent cross-sectional generic template was created, on which the position of the spinal cord, the location of the tonsillar fossa, both pillars on one side, and the posterior pharyngeal wall were identified. A series of normal CT scans was used to create the anatomic template. For each case, the known extent of the primary disease was drawn on the template. In turn, the transparent template was then superimposed on the radiation isodose distribution, using the spinal cord as the common reference. The 90% isodose line was considered to correspond to the treated volume concept described by ICRU (10). The coverage of the tumor by the high-dose region (or treated volume) was evaluated, irrespective of the original intended target volume. Cases were classified into three groups, based on the minimum distance of the 90% isodose line from any part of the tumor defined on the anatomic template. This distance was termed the radiotherapy margin (RT margin). The three categories constituted RT margin groups of < 1 cm, 1–2 cm, or ≥ 2 cm. A finer distinction was not considered feasible, and cases in which doubt existed were categorized on the assumption that the tumor was treated at the next category level (e.g., if doubt about whether the RT margin was < 1 cm, the case was classified as 1–2 cm). In some cases, those classified with RT margin < 1 cm had tumor located outside the 90% line. Patients were considered to have been immobilized satisfactorily, although this has never been formally evaluated for our system.

Statistics and outcomes

The primary endpoint in this study was the occurrence of regional lymph-node failure in the contralateral neck. In addition, the time to regional lymph-node failure, local failure, and time to last follow-up or death were calculated. The calculation of elapsed time for events was dated from the date of initiation of radiotherapy. Those cases failing to demonstrate a complete clinical remission within 3 months of initiation of radiotherapy were deemed to have failed on the first treatment day. The cause of death was used to estimate cause-specific survival, where death from any complications of treatment, or unknown cause, were included as death from disease. Local relapse-free rate, complication-free rates, and cause-specific survival were estimated by the Kaplan–Meier method (11). The impact of salvage treatment following failure in the primary site or the neck is not considered in these results, other than for its contribution to the cause-specific survival result. A multivariate analysis was not performed because the primary endpoint contained too few events (see below).

Crude rates of regional lymph-node failure, including contralateral failure (bilateral or contralateral alone), and local failure were also tabulated against anatomic extent.

Table 1. Modified RTOG/EORTC late radiation morbidity scoring scheme

Organ/Tissue	Grade 3	Grade 4
Mucous membrane	Marked atrophy with complete dryness, telengiectasis, self-limited ulceration	Ulceration requiring surgery
Subcutaneous tissue/muscle	Severe induration or loss of subcutaneous tissue, severe trismus, self-limited necrosis	Necrosis requiring surgery
Bone	Severe pain or tendernesss, self-limited bone exposure	Necrosis, spontaneous fracture

Reproduced with permission from Withers *et al.* (12).

Crude-rate calculation was required because of the small numbers in certain subsets, which made actuarial estimates impossible, and was possible because the extended follow-up provided similar rates for actuarial and crude rates. Fisher's exact test was used to calculate *p*-values for the comparison of two independent proportions. The chi-squared test was used to compare multiple proportions when there were more than two categories in the tabular output.

Radiotherapy complications were graded in the manner used by Withers *et al*. for bone, mucous membrane, subcutaneous tissue, and muscle (12) (Table 1). Only grade 3 or 4 complications were analyzed, as these are unlikely to escape documentation. There were no grade 5 (fatal) radiotherapy complications. Accurate retrospective assessment of less severe complications from the medical records was not feasible because of the subjective nature of these endpoints. They also may not be recorded routinely because they are sequelae that are routinely anticipated. Thus, evaluation of xerostomia was not performed. In addition to being graded, complications were documented with respect to the date of first occurrence to permit actuarial calculations.

RESULTS

Description of cases

In the study period, 228 of a total of 642 patients with carcinoma of the tonsillar region who underwent curative radiotherapy received ipsilateral radiotherapy. From 1970 to 1984, approximately one-third of cases were treated with ipsilateral techniques. This rose to close to one-half of cases in the time period 1985–1991 (Fig. 3a). In 1987, written treatment policies were developed for the radiotherapy of head-and-neck cancer, including the use of ipsilateral irradiation in oropharyngeal cancer. Following this, the proportion of cases treated with "close" radiotherapy coverage of the tumor (i.e., RT margin $<$ 1 cm) dropped from an average of 24% to 6% (3/46) (Fig. 3b).

Males (154, 67.5%) outnumbered females (74, 32.5%). The mean age was 61 years, median 62 years, with a range of 35–94 years. The mean follow-up was 7 years and the median was 5.7 years for those patients not manifesting any local, regional, or distant recurrence. In 150 cases, the disease originated in the tonsillar fossa, in 73 cases, on the anterior pillar, and in 5 cases, the origin was the posterior pillar. Most were well-lateralized lesions, although several had involvement of the middle and medial segments of the hemistructure of the tongue base and soft palate (Table 2). The majority were of early-stage (T1, T2, and N0), but a minority were more extensive lesions. The mean maximum neck lymph-node dimensions were 3.1 cm, with a median of 3 cm and a range of 0.5 to 8 cm, of the 90 node-positive

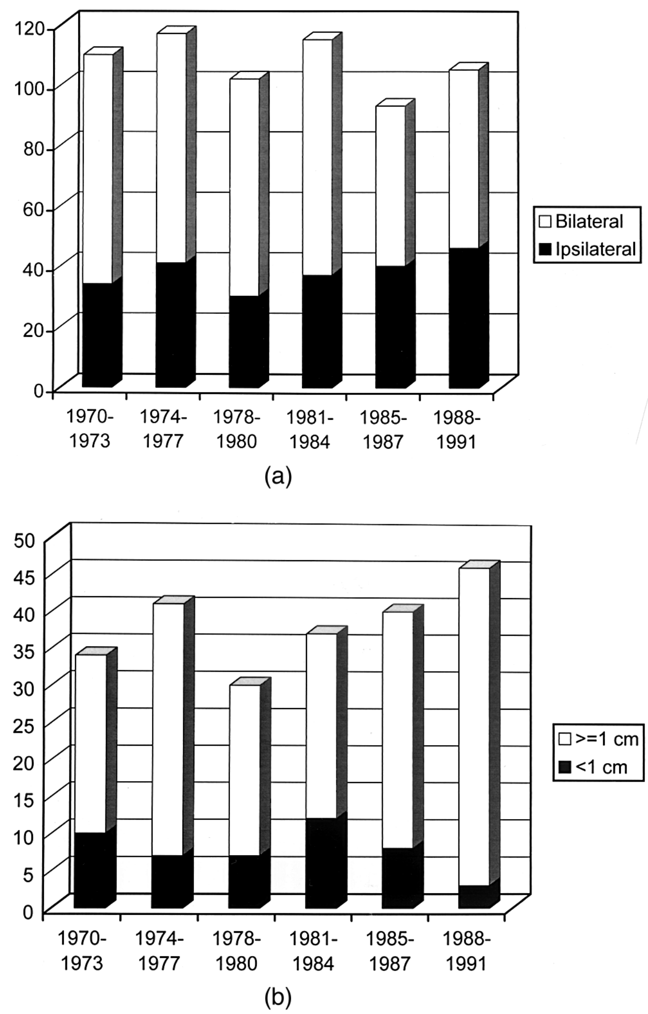

Fig. 3. (a) Numbers of cases of tonsillar carcinoma treated with ipsilateral techniques (of a total of 642 cases treated at PMH in the study period). The vertical axis represents the number of cases treated in the different time periods shown on the horizontal axis. The time groups are based on approximate equal groupings of cases over 21 years. (b) The RT margin status of ipsilateral cases by the same time period groupings shown in (a). The vertical axis represents the number of cases treated with an ipsilateral technique in each time period.

Table 2. Outline of regional lymph node control and side of neck lymph node failure for all cases

Disease extent		Total cases	Lymph node failure by side of neck							
			No neck failure		Ipsi-lateral		Contra-lateral		Bi-lateral	
		n	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
T-category	T1	73	67	(92)	6	(8)	0	(0)	0	(0)
	T2	118	98	(78)	22	(19)	2	(1.5)	2	(1.5)
	T3	30	22	(73)	5	(17)	3	(10)	0	(0)
$p = 0.002$	T4	7	4	(57)	2	(29)	0	(0)	1	(14)
Palate hemistructure involvement	None	146	125	(86)	18	(12)	1	(1)	2	(1)
	Lateral	36	30	(83)	6	(17)	0	(0)	0	(0)
	Middle	29	20	(69)	7	(24)	2	(7)	0	(0)
$p = 0.01$	Medial	17	10	(59)	4	(3)	2	(12)	1	(6)
Base of tongue hemistructure involvement	None	180	152	(85)	24	(13)	2	(1)	2	(1)
	Lateral	39	26	(67)	10	(26)	2	(5)	1	(3)
	Middle	7	5	(72)	1	(14)	1	(14)	0	(0)
$p = 0.17$	Medial	2	2	(100)	0	(0)	0	(0)	0	(0)
N-category	N0	133	123	(92.5)	10	(7.5)	0	(0)	0	(0)
	N1	56	35	(62.5)	13	(23.2)	5	(9)	3	(5.4)
	N2a	28	20	(71.4)	8	(29)	0	(0)	0	(0)
	N2b	8	5	(62.5)	3	(37.5)	0	(0)	0	(0)
$p = 0.00002$	N3	3	2	(66.6)	1	(33.3)	0	(0)	0	(0)
Overall rates		228	185	(81)	35	(15)	5*	(2)	3*	(1)

* Total rate of contralateral failure: 8/228 (3.5%).

patients in whom the size was documented. In 4 cases, no size was available.

Treatment details

The majority of patients (208 cases, 91%) were treated with lateralized ipsilateral-oblique wedge-pair techniques using missing tissue compensators in addition to wedge filters. Thirteen patients (5.7%) received treatment with an ipsilateral electron field with or without an additional photon field, while 7 (3%) were treated with "other" techniques, which weighted the dose strongly toward the ipsilateral side, thereby maintaining the dose to the contralateral neck volume < 35 Gy. The mean minimum dose to the ipsilateral target volume (i.e., that defined by the treating radiation oncologist) was 49.6 Gy, typically administered over 4 weeks as daily treatment fractions. The mean maximum dose 54.9 Gy, the mean nominal dose was 51.5 Gy, and the TAD was 52.7 Gy. The median dose to the center of the contralateral neck volume (and therefore the opposite parotid gland) was 12.7 Gy, the mean was 13.6 Gy, the minimum was 4.2 Gy, and the maximum was 25.5 Gy. The majority of cases received 50 Gy in 20 fractions on consecutive days over a 4-week period prescribed, to the tumor as noted in the "Methods" section.

The most common beam energy was cobalt (74.5% of cases); 19.5% were treated with 6 MV, and the few remaining cases received electrons alone or mixed with photons. The mean and median field length was 11 cm (range 6.5–15 cm) for the 133 N0 patients, and the corresponding value for the 95 cases in the N-positive group was 12 cm (range 8.5–16 cm). Immobilization in a plaster or plastic shell was employed in 196 patients (86%).

Regional lymph-node control by N-status

The 3-year overall actuarial regional lymph-node relapse-free rates and crude regional control rates were (Table 2): overall rate: 80% and 185/228 (81%); N0 rate: 91% and 123/133 (92.5); N1 rate: 63.5% and 35/56 (62.5); N2 rate: 67% and 25/36 (69%); N3: 67% and 2/3 (66.7%), respectively. The rates were higher for cases where the primary tumor never failed (Table 3).

Contralateral neck failure occurred in eight patients. In three cases, the failure was in the neck alone; however, in five, the failure coincided with or was preceded by failure at the primary site. Of the five with combined primary and neck failure, three were also bilateral neck failures. No patient with N0 disease failed in the opposite neck (Table 2).

The impact of primary tumor and neck disease extent on contralateral failure

While only 8 failures in total occurred in the contralateral neck, and no contralateral failure was seen in any patient with N0 disease, it is also notable that the extent of the primary may also be important. For example, no contralateral failure was seen in any T1 case, irrespective of the nodal status (Table 2). Of the 3 patients who experienced failure in the contralateral neck volume with the primary controlled, all had significant palate involvement (to within 1 cm of midline in 2 cases, and involving the middle hemistructure of the palate in the third case). Thus, all 3 had high-risk primaries coupled with positive neck disease. The percent failure in the contralateral neck according to increasing degrees of medial extension from the tonsillar region is shown (Table 4). Cases are divided into those with no involvement of tongue base or palate, cases involving

Table 3. Outline of regional lymph node control and side of neck lymph node failure with primary controlled

Disease extent		Total cases	Lymph-node failure by side of neck							
			No neck failure		Ipsilateral		Contralateral		Bilateral	
		n	n	(%)	n	(%)	n	(%)	n	(%)
T-category	T1	67	61	(91)	6	(9)	0	(0)	0	(0)
	T2	86	78	(91)	7	(8)	1	(1)	0	(0)
	T3	21	16	(76)	3	(14)	2	(10)	0	(0)
$p = 0.002$	T4	2	2	(100)	0	(0)	0	(0)	0	(0)
Palate hemistructure involvement	None	118	109	(92)	9	(8)	0	(0)	0	(0)
	Lateral	24	23	(96)	1	(4)	0	(0)	0	(0)
	Middle	22	17	(77)	4	(18)	1	(5)	0	(0)
$p = 0.01$	Medial	12	8	(67)	2	(16.5)	2	(16.5)	0	(0)
Base of tongue hemistructure involvement	None	151	135	(89)	15	(10)	1	(1)	0	(0)
	Lateral	20	18	(90)	1	(5)	1	(5)	0	(0)
	Middle	4	3	(75)	0	(0)	1	(25)	0	(0)
$p = 0.17$	Medial	1	1	(100)	0	(0)	0	(0)	0	(0)
N-category	N0	103	100	(97)	3	(3)	0	(0)	0	(0)
	N1	41	32	(78)	6	(15)	3	(7)	0	(0)
	N2a	24	19	(79)	5	(21)	0	(0)	0	(0)
	N2b	5	4	(80)	1	(20)	0	(0)	0	(0)
$p = 0.00002$	N3	3	2	(67)	1	(33)	0	(0)	0	(0)
Overall rate with primary controlled		176	157	(89)	16	(9)	3*	(1.7)	0	(0)

* Total rate of contralateral failure: 3/176 (1.7%).

these structures individually, or those involving both the soft palate and base of tongue. Although the number of cases involved are few, an increase in failure rate in the contralateral neck may exist when one compares those cases without involvement of either structure and a negative neck (no contralateral failures), to the highest rate found if both palate and tongue base are involved in a node-positive neck (21% contralateral failure, or 3 of 14 cases; Table 4). Intermediate levels of risk seem apparent among the other node-positive situations, with none of the N0 cases demonstrating contralateral failure. However, it is stressed that only 3 patients with control at the primary site failed in the contralateral neck (Table 3).

Local control and cause-specific survival

The 3-year overall actuarial local relapse-free rate and crude local control rates in this selected series are as follows: overall rate: 76.7% and 176/228 (77%); T1: 92.8% and 67/73 (92%); T2: 73.1% and 67/73 (73%); T3: 68.6% and 21/30 (70%); and T4: 28.5% and 2/7 (29%), respectively (Fig. 4). T3 disease behaves similarly to T2 disease, at least from the standpoint of local control in this selected series.

The extent of coverage of the primary disease by the high-dose volume (defined as the 90% isodose) is linked to worse local control for cases with an RT margin < 1 cm (30% local control) compared to those with RT margin ≥ 1 cm ($p < 0.0001$) (89% local control) (Table 5).

The 3-year cause-specific survival was 76%, which included the impact of salvage treatment.

TN groupings and local and regional control

Because no multivariate analysis was possible to provide relative risk estimates for the contralateral-neck failure endpoint, we present the regional and local control rates for each of the four T-categories presented by four N-categories (N0, N1, N2, N3) as aggregated T- and N-categories (TN group) (Table 6). The main points have already been noted (i.e., the absence of contralateral failure in any T1 or N0

Table 4. Percent failure in contralateral neck involvement of primary tonsillar tumor in palate and/or base of tongue

Involvement of palate and/or BOT	Total cases	N0 neck		N+ neck		Overall	
		n	(%)	n	(%)	n	(%)
None	121	0	(0)	2/52	(3.8)	2/59	(1.6)
Palate alone	59	0	(0)	2/21	(9.5)	2/59	(3.4)
BOT alone	25	0	(0)	1/7	(14)	1/25	(4)
BOT and palate	23	0	(0)	3/14	(21)	3/23	(13)
Overall	228	0	(0)	8/94	(8.5)	8/228	(3.5)

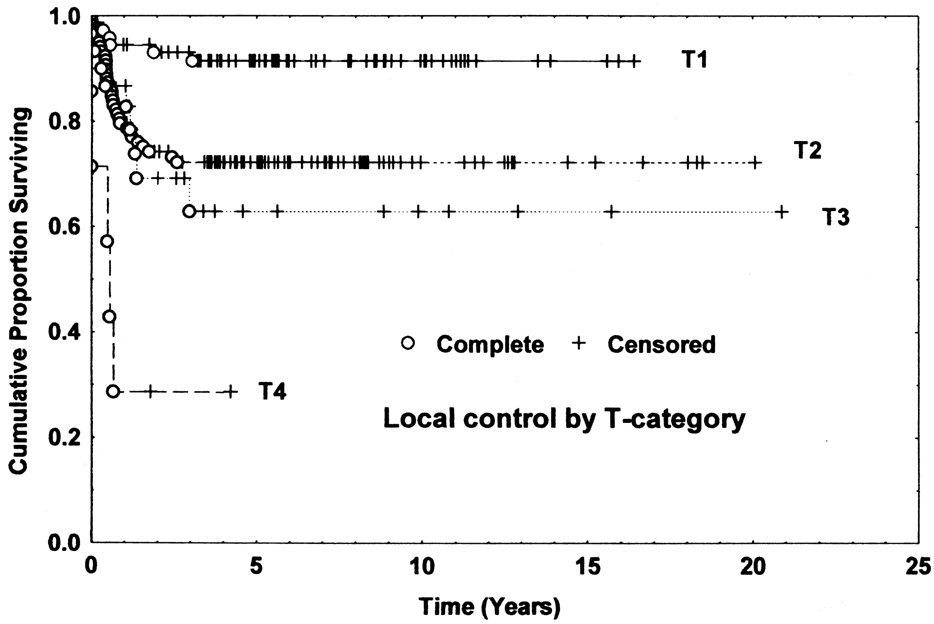

Fig. 4. Actuarial local relapse-free rate for all cases of tonsillar region carcinoma treated with ipsilateral techniques. The results are shown by T-category. The overall local control was 77% in this selected series.

case and only 8 failures in total and 3 with primary controlled). The selected nature of the population may explain the restriction of all 8 contralateral failures to the N1 category rather than higher-risk N-categories. Thus, of the 30 node-positive T1 cases, only 7 (23%) were N1; the remaining 22 being N2 and N3 disease (Table 6). The potential risk of contralateral failure in higher N-categories appears ameliorated by the lower risk associated with the favorable T1 category. In contrast, of 155 T2–T4 cases, N1 disease was represented more than other N-categories. Thus, of 64 cases in the T2–T4 N-positive group, 47 (73%) were N1 disease, with the more advanced N-categories being less prominent, especially N3, where there was a sole case (Table 6). Consequently, the N1 category for these patients is prejudiced by its association with more advanced T-category disease, placing them at higher risk of contralateral failure. Finally, of the few patients with contralateral failure, only 1 patient was salvaged (see footnote for Table 6).

Complication rates

The overall 5-year actuarial rate of complications attributed to radiotherapy was 89% (see Fig. 5). For individual toxicities, the 5-year actuarial risk of grade 3 to 4 toxicity were: mucosa (3.4%), subcutaneous tissues and muscle soft tissue (0.5%), and bone (7%). Of the 15 bone complications in the series, 14 took place before 1984, for a rate of 10.4% (14/135) in that interval, compared to 1/93 (1%) for the subsequent cases. For the period until 1984, bone complications were generally related to dental practice at the time. Six of the 14 were grade 3 and 8 were grade 4 bone toxicity. Of the 6 patients with grade 3 toxicity, all 3 had undergone multiple tooth extractions before radiotherapy, 1 had multiple teeth extracted during radiotherapy, 1 had an ill-fitting denture, and 1 experienced self-limited bone exposure following successful surgical salvage with composite mandibular resection of a primary site failure. Of the 8 grade 4 complications, 5 had undergone multiple tooth extractions before radiotherapy, 1 had multiple teeth removed during radiotherapy, in 1 there was no apparent cause (the patient had refused any dental treatment), and for the final case, we did not record data about risk on the study sheet. The sole complication (a grade 3 toxicity) in the later period appeared to occur under the hot spot of the wedge (52.5 Gy delivered in 4 weeks). The patient had an existing sinus in the external auditory canal and was classified as "self-limited bone exposure," which eventually resolved 30 months following the completion of radiotherapy.

Table 5. Local control by size category of RT Margin

RT margin	Total No.	No. controlled	control %
$<$ 1 cm	47	14	30
1–2 cm	110	95	86
$>$ 2 cm	71	67	94
Total	228	176	77

$p < 0.0001$.

DISCUSSION

Generally, elective neck irradiation is not recommended where the risk of subclinical disease is less than 10%, because of the morbidity of radiotherapy, especially arising from damage to salivary tissue (13). This study demonstrates that the failure rate in the opposite neck is very rare in cases with carcinoma of the tonsillar region selected for

Table 6. Crude local and regional lymph-node control rates with side of lymph node failure in the neck

	Local control		Regional control		Lymph node failure by side of neck relapse		
T- and N-group	*n*	(%)	*n*	(%)	Ipsilateral only	Contralateral	Bilateral
T1N0	39/43	(91)	42/43	(98)	1	0	0
T1N1	7/8	(88)	8/8	(100)	0	0	0
T1N2	19/20	(95)	15/20	(75)	5	0	0
T1N3	2/2	(100)	2/2	(100)	0	0	0
T2N0	57/75	(76)	68/75	(91)	7	0	0
T2N1	22/32	(69)	18/32	(56)	10	2*	2†
T2N2	6/10	(60)	6/10	(60)	4	0	0
T2N3	1/1	(100)	0/1	(0)	1	0	0
T3N0	7/14	(50)	13/14	(93)	1	0	0
T3N1	10/11	(91)	6/11	(55)	2	3‡	0
T3N2	4/5	(80)	3/5	(60)	2	0	0
T3N3	—	(—)	—	(—)	—	—	—
T4N0	0/1	(0)	0/1	(0)	1	0	0
T4N1	2/5	(40)	3/5	(60)	1	0	1§
T4N2	0/1	(0)	1/1	(100)	0	0	0
T4N3	—	(—)	—	(—)	—	—	—
Total	176/228	(77)	185/228	(81)	35	5	3

Data are grouped by T- and N-categories (UICC 1992).
* One of two cases had failure at the primary site prior to failure in the opposite neck.
† Both failed initially at the primary prior to failure in the opposite neck. In one, first failure was in the ipsilateral neck, followed by primary failure before eventual opposite neck failure.
‡ One of three had initial failure at the primary site. This was the only case salvaged and death resulted from a new primary 3 years later; the other two failed only in the opposite neck.
§ This case failed at the primary, with concurrent failure in both necks.

management using techniques that withhold comprehensive radiotherapy to the contralateral neck. Although an overall rate of 3.5% (8 of 228 cases) was seen, this is even smaller in cases where the primary was controlled (1.7%, or 3 of 176). In this study, no patient with N0 disease failed in the opposite neck, nor did any patient with T1 disease. Node-positive patients with lateralized lesions have a moderate risk of contralateral failure and this risk must be balanced against the long-term morbidity of xerostomia using bilateral techniques. Of interest, the results of the present series and two additional recent reports are very similar (4).

The major benefit of ipsilateral radiation treatment for

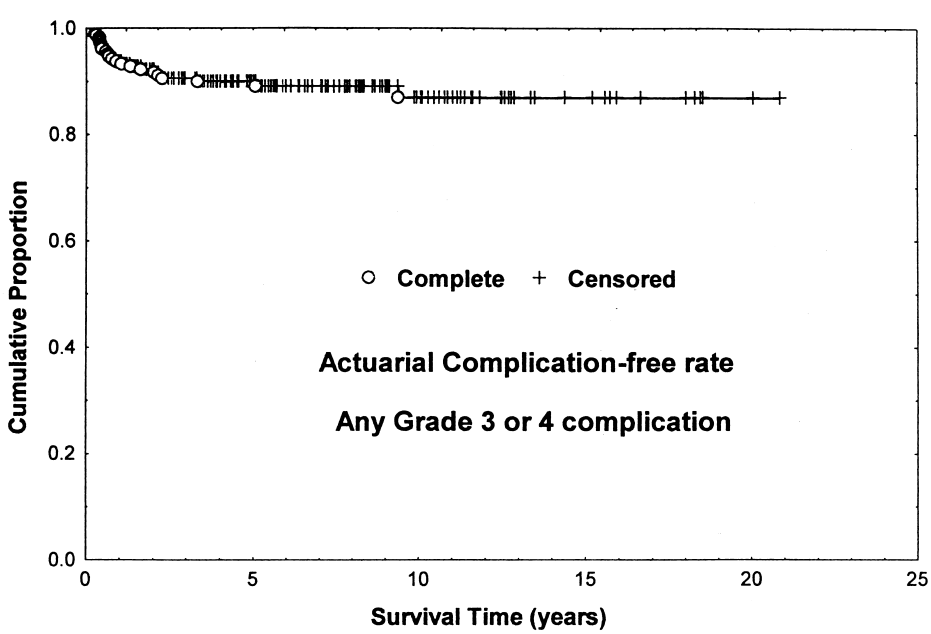

Fig. 5. Actuarial complication-free rate for all grade 3 and 4 complications. See Table 1 for definitions. For individual complications, see “Results” section.

carcinoma of the tonsillar region is to provide the opportunity for salivary protection by exclusion of dose to the contralateral parotid gland. A variety of methods already exist or are being evaluated to attempt to ameliorate the problem of xerostomia from parotid irradiation. These include pharmacologic (14–16) and radioprotective strategies (17, 18), and surgical relocation of salivary tissue (19). None is uniformly satisfactory and, therefore, avoidance of irradiation of major salivary tissue when possible remains an important approach.

Radiotherapy techniques, in particular recent innovations in intensity-modulated radiotherapy (IMRT) and conformal radiotherapy, offer opportunity for more precise targeting and sparing of salivary tissue (20–23). In general, such plans have been applied to situations where both sides of the neck are treated, although they could be deployed for lateralized lesions. The present paper, like those of others (2, 4, 5), discusses evidence for complete exclusion of contralateral irradiation in selected cases of carcinoma of the tonsillar region, and which would have wider appeal, given that IMRT and conformal techniques are not universally available.

While exclusion of the parotid gland from the target area is a major advantage, one of the pitfalls is inadequate coverage of the primary tumor (6, 9). Although failure patterns in relation to the field coverage and sites of primary failure would be of interest, we did not feel confident about making this judgment retrospectively. On the other hand, we felt a description of tumor coverage by the high-dose volume was possible based on the original treatment dosimetry and the description of disease extent (see "Methods" section). As shown in the results, adequate coverage had historically been a problem, although the risk was negligible in the most recent years of the study (Table 2). Of the three cases in the 1988–1991 era, one in fact had adequate coverage using an ipsilateral wedge pair for most of the course; however, a final boost was administered with an intraoral cone to minimize acute morbidity in a frail 80-year-old patient. The use of an intracoral-cone boost constituted the reason for the "close" ($<$ 1 cm) classification of the RT margin. The change to better coverage of the target volume coincided with the introduction of written policies for the management of head-and-neck cancer at the PMH. The policies indicated the need to focus on coverage of 2 cm of clinical target volume (CTV) surrounding the gross treatment volume (GTV). Whether this was coincidental, or truly raised awareness about the importance of coverage will remain speculative. Nevertheless, because of this, the practice of planning 3D volumes without CT planning has been abandoned at PMH.

The advantages of CT planning are to promote greater diligence and accuracy in ensuring that tumor coverage is adequate, while at the same time, sparing the contralateral parotid (5, 21, 24). This is especially important because the parotid gland size, configuration, location, and anatomic relationship to other structures may vary (25, 26). In all cases, we now employ CT simulation where the GTV is first contoured. A CTV is then defined to permit a minimum of 1 cm of CTV around all tumor. Frequently, however, the margins of CTV around the GTV are greater than this. Particular care is taken to cover disease extending to the posterior pillar, which creates the greatest difficulty in these cases, because of the need to protect the spinal cord and brainstem from the posterior oblique beam. The medial edge of the posterior oblique beam risks passing dangerously close to the GTV if this form of posterior extension is present. The shape of the typical distribution of a wedge-pair technique can also be problematic, especially in the way it points narrowly in the medial part of the volume (see Fig. 1). Thus, care must also be taken to avoid geographic "miss" in medially extending disease on the soft palate or tongue base when using only two beams (e.g., an anterior and posterior oblique arrangement). An alternative technique is the use of a third beam from the contralateral side to maintain dose medially in the volume (4). We have not used the third beam because of our goal in sparing contralateral parotid from excessive dose on the opposite side, which may result in at least 18% of the prescribed dose being delivered to the opposite parotid (4).

Currently, we contour vulnerable tissues on the CT simulator, including the contralateral parotid and the lips anteriorly. Ocular structures are also defined in the event that exit dose may be directed toward them, in addition to spinal cord and brainstem. Ordinarily, patients are positioned and masked before CT simulation, with the neck extended to permit the eyes to be positioned away from the beams. Our current goal is to exclude the contralateral parotid entirely from either beam. This is accomplished by directing the anterior oblique beam more posteriorly than had been our practice previously, thereby avoiding the opposite parotid completely. Beam's-eye-view (BEV) projections are used to collimate the beam to protect the lips whenever possible from the posterior oblique beam to minimize severe acute reactions, especially in the region where both beams may overlap. This is especially important at the ipsilateral oral commissure. At all times, the adequacy of coverage of the GTV by the CTV must be verified on the BEVs.

Cross-sectional imaging was not performed in this study, except with some of the most recent cases. However, unlike many retrospective series in which accurate descriptions of the tumor may be problematic, the description of the tumors in this series was made possible by the prospective documentation of disease extent in combined clinics attended by head-and-neck surgeons and radiation oncologists throughout the period of the study. Tumor extent was documented on "tick sheets" jointly by the surgeon and radiation oncologist and signed by the treating oncologist. These forms, developed at the Ontario Cancer Registry and used at PMH and the other Ontario cancer clinics since the 1960s, were the predecessors of the staging forms used by the UICC and the AJCC. Examples for several of the present study cases are shown (27). Despite the limitation of absence of CT or MRI, the error in case descriptions is still likely to be one of "underestimation" rather than an overestimate of disease extent. Thus, the problem with adequacy of the disease coverage may be even greater than is described. An additional problem is the potential for setup error that is not considered in the present study. Unilateral techniques are likely more vulnerable to variability because small systematic deviations are possible (28). However, it is important to recognize that despite the potential limitations in planning in the series, the contralateral neck failure rate remained exceptionally low.

The majority of bone complications in the study resulted from inappropriate dental management in the early period of the study. The incidence of post-radiation dental complications became extremely rare in the second part of the study. The reasons for this are reviewed, but included in particular, abandoning the practice of extraction of all teeth encompassed by the radiation field (29). However, concern exists about whether "hot spots" under the thin edges of the wedges in wedge-pair techniques will contribute to a heightened incidence of bone toxicity (7). This was most likely minimized in our study by the combination of moderate-dose radiotherapy (generally 50 Gy in 4 weeks) and the fact that most patients had customized 3D missing-tissue compensators to promote dose homogeneity in the volume. Currently, our doses are typically higher than in the past (e.g., 66–70 Gy as daily fractionation or with altered fractionation). To ensure that doses are maintained safely, we would normally reduce fields at 50 Gy when possible so that the final cone-down boosts treat smaller volumes of bone. In addition, compensators continue to be used; however, cases are also treated with beam segmentation using multileaf collimation (MLC) techniques, which provide efficient means of optimizing dose homogeneity. In some cases, multiple field plans to the ipsilateral side may also be preferable in the higher-dose protocols (7).

Because of the time period over which the study took place, we lack objective information about salivary function in these cases. Using similar techniques to those used in our study, Leslie and Dische showed only a modest reduction in stimulated parotid flow at 3 months in glands receiving 10–14 Gy compared to those receiving > 40 Gy where the reduction was marked (30). We calculated the mean dose to the opposite parotid to be 13 Gy, which should be associated with substantial functional recovery of the parotid (23, 31).

Our recommendations are to continue to advocate ipsilateral radiotherapy in many cases of carcinoma of the tonsillar region. However, reasonable selection criteria should be considered before proceeding with this plan. We support the observation that the outcome cannot be compared to patients treated with a bilateral technique because the two groups are dissimilar, and the decision to use either treatment approach was not performed randomly (4). Nevertheless, the data are presented to be available for comparison with the results of others and for the benefit of those considering the ipsilateral approach (4). In addition, our policy is to discuss the data with appropriately selected patients before proceeding, because a decision to accept permanent morbidity from bilateral parotid irradiation rests with the patient. Our usual criteria are to regard all lateralized lesions as candidates for this approach. We would ordinarily recommend unilateral irradiation to patients with only small amounts of extension to the soft palate or base of tongue. For the latter, disease confined to the mucosa and with no more than 1 cm of medial extension is considered safe. A similar extent of soft palate extension is also reasonable. More medial extension likely heightens the risk, although it is still modest according to the data. Again, we would caution that great care should be taken to encompass the GTV by at least 1 cm of high-dose volume. Care must be taken to include the medial disease on the palate or tongue base, but also disease extending onto the posterior pillar or posterior pharyngeal wall. In general, we regard the latter as a relative contraindication to these techniques because of the difficulty encompassing such disease. Any case of established regional lymph-node involvement appears to have a modest risk, probably ranging from 5% to 20% of failure in the contralateral side if we include those cases where failure at the primary site took place.

In summary, ipsilateral radiotherapy is an effective approach for the majority of cases of lateralized carcinoma of the tonsillar region. Certain selection criteria have been noted and should be observed. Patients should be involved in the decision to use these techniques in cases where the risk is moderate (e.g., those with established regional node disease). When using these techniques, we feel that appropriate cross-sectional imaging should be performed as part of the staging procedures and the approach should be complemented by the use of CT planning with 3D techniques. This is probably accomplished best with CT simulation using the principles outlined. The benefits remain compelling for patients in that salivary function can be protected. On the other hand, it is crucial to avoid underdosage of disease, both at the primary or regional lymph node regions at risk.

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