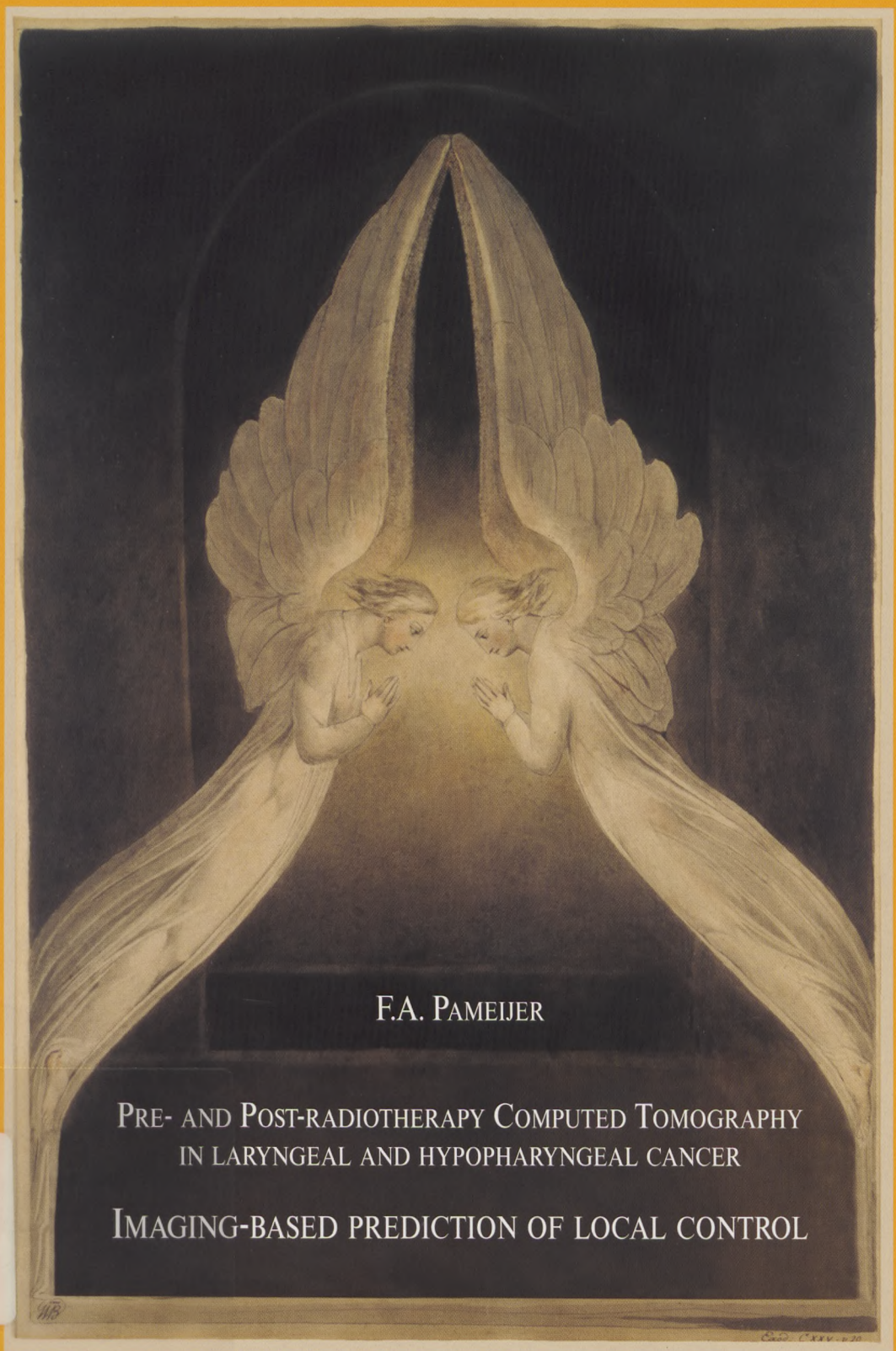

F.A. PAMEIJER

PRE- AND POST-RADIOTHERAPY COMPUTED TOMOGRAPHY IN LARYNGEAL AND HYPOPHARYNGEAL CANCER

IMAGING-BASED PREDICTION OF LOCAL CONTROL

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IMAGING-BASED PREDICTION OF LOCAL CONTROL

F. A. PAMEIJER

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PRE- AND POST-RADIOTHERAPY COMPUTED TOMOGRAPHY IN LARYNGEAL AND HYPOPHARYNGEAL CANCER

IMAGING-BASED PREDICTION OF LOCAL CONTROL

(with a summary in Dutch)

Pre- en post-radiotherapie computer tomografie bij larynx en hypofarynx kanker
Voorspelling van de kans op lokale tumor controle, op basis van beeldvorming

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van de Rector Magnificus, Prof. Dr. H.O. Voorma,
ingevolge het besluit van het College voor Promoties
in het openbaar te verdedigen op
dinsdag 9 november 1999 des namiddags te 16.15 uur

door

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Contents

Aan mijn Ouders

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CHAPTER 1

Introduction and aims of the thesis

INTRODUCTION AND AIMS OF THE THESIS

Demographics

Cancer of the larynx comprises about 2% of the total number of human cancers, and is the most common head and neck cancer (skin excluded). The number of new cases in 1993 in the United States is estimated at 12,600 (male to female ratio 4:1) with an estimated 3,800 deaths due to laryngeal cancer.[1] In the Netherlands, 689 new cases of laryngeal cancer were recorded in 1994 with 230 deaths due to this disease. The annual incidence in males approximates 8 per 100,000 persons.[2] Laryngeal cancer seems to be primarily related to cigarette smoking.[3] The importance of alcohol in the etiology of laryngeal cancer remains unclear, but it is probably less important than in cancer in other head and neck sites.[4]

Hypopharyngeal cancer, with an annual incidence of 1.3 per 100,000 (male) persons, occurs less frequently than laryngeal carcinoma.[2] Cancers of the pyriform sinus constitute the majority of hypopharyngeal tumors, comprising 65 to 75% of reported tumors.[5] Predisposing factors are tobacco and alcohol abuse.[6]

Treatment options

The optimal management of patients with laryngeal and hypopharyngeal carcinoma is still a matter of research. Traditionally, surgery and/or radiotherapy (RT) are the curative treatment options for carcinoma arising in the head and neck. Chemotherapy used alone is not curative, and its role as an adjunct to surgery, RT, or both is under investigation.[7-13]

The majority of surgically treated patients undergo a radical procedure; e.g. total laryngectomy (laryngeal carcinoma) or total laryngectomy and (partial) pharyngectomy (hypopharyngeal carcinoma).[14-16] In these procedures the tumor is removed, including the entire larynx. As a consequence, the patient is cured of his/her cancer with the loss of his/her natural voice.

The average treatment with RT consists of a five- to seven-week period with once- or twice-daily irradiation.[17-19] RT allows for preservation of laryngeal function, including the voice.

In a minority of cases 'organ preserving' surgery, e.g. hemi- or supraglottic laryngectomy (for glottic/supraglottic carcinoma) may offer the option of preserving (partial) laryngeal function.[15,16,20] However, in most patients the lesions are too advanced at the time of presentation to be suitable for this type of surgery.

In selecting the optimal treatment modality for a patient with squamous cell carcinoma of the larynx, the main goal is cure with the best functional results and

the least risk of a serious complication. For purposes of treatment planning, patients may be considered to be in either an early group (small tumors) or a late group (advanced tumors). The early group may be initially treated by RT or, in selected cases, by partial vertical or horizontal laryngectomy. The late group may be treated by RT, with salvage laryngectomy reserved for local recurrence, or with total laryngectomy with or without post-operative irradiation.[21]

For the subsites considered in this thesis; glottic larynx (T3), supraglottic larynx (T1, T2, and early T3) and pyriform sinus (T1, T2), surgery with or without post-operative RT or RT alone are both suitable as curative treatment options.[17-19] The choice between these two options presents a dilemma. In surgery, the tumor is removed, including the entire larynx. RT allows preservation of laryngeal function, including the voice. However, if irradiation fails and the patient develops a local recurrence he/she has endured a five-to seven-weeks course of (unnecessary) high-dose RT. Surgical salvage, which is then the only therapeutic option left, will still result in the loss of voice, and these patients are at risk of developing major complications, including pharyngocutaneous fistula due to wound dehiscence.[18] More accurate selection of patients who are likely to be cured with definitive RT is therefore needed. Identification of patients who are likely to be cured with definitive RT will reduce the fraction of patients undergoing salvage surgery, and may improve current local control rates. This requires a staging system that categorizes patients in different stage groups with differences in prognosis and corresponding therapeutic options.

Staging

Clinically, head and neck tumors are staged by the TNM classifications developed by the American Joint Committee on Cancer and the International Union Against Cancer ("T" stands for primary tumor, "N" for regional lymph nodes, and "M" for metastasis). As in other parts of the body, the T-stage is used to describe the local extent of tumors in the various subsites of the head and neck (T1 -T4), the N-stage describes metastatic disease of the regional lymph nodes (N0 - N3) and the M-stage refers to the presence (M1) or absence (M0) of distant metastases.[22,23]

For other parts of the body, such as lung and breast, the T-category is governed principally by tumor size.[23] In the upper and lower digestive tract, the amount of intestinal wall invasion is the most important parameter determining T-stage.[23] T-staging of laryngeal and hypopharyngeal carcinoma depends mainly on location in different anatomical subsites and vocal cord fixation.[23]

It has become clear that, while the TNM classification system allows statistical analysis of groups of patients and exchange of data between oncological centers, it seems to have limitations in serving as a guideline in the management of a particular patient with laryngeal or hypopharyngeal cancer.[24,25] Originally, TNM-classifications were based on endoscopic and other clinical findings which may fail to define the true three-dimensional tumor bulk.[26] Radiological findings were allowed to be used in staging as of 1987, but before computed tomography (CT) became widely available the results from imaging were often tenuous since one had to rely on soft tissue views and tomograms.

Choice of imaging modality

Modern imaging techniques, especially CT and MRI (magnetic resonance imaging), can be used to supply information on deep tumor spread that cannot be appreciated clinically. The role of CT for imaging laryngeal and hypopharyngeal carcinomas has continued to evolve over the last ten years. This is a result of technological advances that have decreased scan acquisition time, and otherwise improved our ability to obtain high resolution, thin section (1-3 mm) images, permitting a detailed evaluation of the laryngeal anatomy free of motion artifacts. Several studies have been performed correlating CT findings of laryngeal carcinoma with whole organ sections. These studies have shown that CT can accurately predict the site, size, and deep spread patterns (except for lesions limited to the mucosal lining) of laryngeal tumors.[27-31] Pretreatment imaging has been shown to improve the accuracy of clinical staging, and has become generally accepted as an adjunct to the physical examination for evaluation of laryngeal tumors at many institutions.[28-34]

The question of which modality, CT or MRI, is the method of choice in imaging of the larynx and (hypo)pharynx has not yet been answered definitively. This is still an on-going debate. Previous histopathological studies suggested superiority of MRI over CT in delineating the site and the extent of laryngeal cancer.[35] In more recent histopathological investigations, no significant difference was demonstrated between MRI and CT, both combined with clinical evaluation in pretherapeutic staging of laryngeal and hypopharyngeal carcinoma.[33,34] In an editorial, Som discussed 'the present controversy over the imaging method of choice for evaluating the soft tissues of the neck'.[36] He analyzed 'pros and cons' of CT and MRI with respect to criteria that reflect the problems posed by the present medical environment. These include provision of sufficient information to allow the most informed treatment planning by clinicians, easy and accurate interpretation by the majority of

radiologists, the number of patients studied in a given time period, and cost-effectiveness. He concludes that a well-monitored, contrast-enhanced CT study is the clear winner, finishing at the top of these criteria in virtually all instances.[36]

For laryngeal and hypopharyngeal tumors, we follow the approach advocated by Mancuso et al.[37], with CT as a first choice. In approximately 10% of cases, an additional MRI study is needed to resolve specific issues that would have consequences for treatment; e.g., spread across the laryngeal ventricle (glottic/supraglottic carcinoma) or submucosal spread toward the esophageal inlet (hypopharyngeal carcinoma).

Value of pretreatment imaging parameters for prediction of local control after definitive RT

In addition to exquisite display of anatomy, recent studies have shown that certain imaging parameters identified on CT and MRI studies may predict the local outcome of patients with laryngeal carcinoma treated with definitive RT.[38-42] Important imaging parameters that were identified included the involvement of specific sites, depending on the location of the primary tumor, cartilage abnormalities and tumor volume.

The insight that tumor volume is of great importance in predicting the likelihood of primary tumor control with definitive RT is not new. As early as 1971, Fletcher recognized that the volume of disease (and not its arbitrary stage) was the key factor in predicting the likelihood of primary tumor control in squamous cell carcinoma of the uterine cervix treated with definitive radiotherapy.[43] In the head and neck, Gilbert et al., in 1987, were the first to use CT to correlate tumor volume with local control in a group of 37 patients with laryngeal carcinoma (T2 or greater) treated with curative RT.[38] The study suggested that tumor volume is a significant factor in determining the outcome of primary RT in advanced laryngeal carcinoma. Subsequent reports have confirmed the positive correlation between tumor volume and prognosis in the larynx and other subsites of the head and neck.[39,40,44-48]

Value of posttreatment imaging parameters for prediction of local control after definitive RT

Clinical examination of the larynx after RT is difficult, because of radiation effects which alter the mucosa and produce varying degrees of edema and fibrosis. Residual or recurrent tumor can therefore be difficult to detect by physical examination. However, early detection of recurrence is crucial if salvage therapy is to be initiated. Radionuclide studies have shown potential in this regard.[49-57] Preliminary experience

suggests that results of CT seem useful for prediction of local control after radiation treatment. In this report, Mukherji et al. suggested imaging-based criteria for separating routine postradiation changes from significant focal masses.[58,59]

Aims of the thesis

The studies mentioned above inspired us to investigate the possible role of pre- and post-RT CT in the evaluation of the primary site in patients with laryngeal and hypopharyngeal cancer, and to determine which imaging parameters can be used as predictors of local control. Ideally these CT-based parameters, either alone or in combination, should be able to stratify patients into those in whom permanent control at the primary site is very likely (favorable), and those in whom it is much less likely (unfavorable).

We started by analyzing tumor volume variability in a group of patients with similarly staged (T3) head and neck tumors, using CT-based tumor volume measurements (summation-of-areas technique) *(Chapter 2)*. Then, we investigated whether pretreatment CT can predict local control in patients with squamous cell carcinoma of different laryngeal and hypopharyngeal subsites, treated with RT alone *(Chapters 3-5)*. Finally, we assessed the value of post-RT CT-findings for prediction of local control in laryngeal cancer *(Chapter 6)*. This thesis concludes with a general discussion and an assessment of future perspectives *(Chapter 7)*.

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CHAPTER 2

Variability of tumor volumes in T3-staged head and neck tumors

Frank A. Pameijer, Alfons J.M. Balm, Frans J.M. Hilgers, Sara H. Muller

Head and Neck 1997; 19:6-13

ABSTRACT

Background

The Tumor Node Metastasis (TNM) classification system describes head and neck tumors using anatomic or unidimensional criteria and may therefore fail to define the actual three-dimensional tumor bulk. To investigate this we measured variability of tumor volumes (**V**vol.) in T3 staged head and neck tumors.

Materials and Methods

Patient material consisted of pretreatment computerized tomography (CT) scans of 71 patients, seen between 1990 and 1995, with T3 head and neck carcinoma involving different subsites. CT scans of 42 patients displayed distinct tumor boundaries and were free of motion and/or dental artifacts. Using these scans, tumor volumes were measured using the summation-of-areas technique, and **V**vol. was determined.

Results

Following are the tumor volume measurements: T3 larynx carcinoma (n = 12) **V**vol, 1.7-17.0 cm^3 (median 3.7 cm^3); T3 oropharynx carcinoma (n = 13) **V**vol, 10.0-41.2 cm^3 (median 18.3 cm^3); T3 hypopharynx carcinoma (n = 10) **V**vol, 8.9-67.8 cm^3 (median 17.4 cm^3); T3 nasopharynx carcinoma (n = 3) **V**vol, 3.7-30.1 cm^3; T3 maxillary sinus carcinoma (n = 4) **V**vol, 56.0-103.1 cm^3.

Conclusion

T3-Staged tumors of the head and neck show considerable variability of tumor volumes. Incorporation of tumor volume data may further refine the TNM staging system.

INTRODUCTION

The Tumor Node Metastasis (TNM) classification was introduced in 1944 by Pierre Denoix.[1] At present, it is the most commonly used system for describing various tumors and their regional and distant metastases. Classification of patients with the TNM system makes it possible to compare and exchange data between oncological centers.

In the head and neck region, as in other parts of the body, application of the TNM system variables further enables the clinician to categorize patients into stage groups I to IV. These stage groups are associated with differences in prognosis and usually with different treatment options. Ideally, they should contain patients with the same prognosis, resulting in maximal discriminative value of the survival curve.

T-Staging depends mainly on location in different anatomical regions and subsites and/or maximal diameter of the primary tumor. Concerning the criteria based on location; a low volume (prognostically favorable) tumor in the nasopharynx, supraglottic larynx, or hypopharynx being present in more than one subsite receives automatically a higher T-stage than an voluminous tumor limited to one subsite. In the same fashion low and high volume tumor masses could very well be classified in the same T-stage if their location is identical. Staging based on maximum diameter is questionable. For example, superficially spreading oropharyngeal carcinoma frequently exceed 4 cm in greatest diameter: T3, without any deep infiltration. This results in a low-volume tumor with a high T-stage.

Various reports in the literature to date have recognized a positive correlation between tumor volume and prognosis for all subsites of the neck.[2-8] Recently Johnson et al.[2] criticized the TNM classification in the head and neck region because T-staging remains dependent upon subjective and unidimensional criteria which may fail to define the true three-dimensional tumor bulk.

To investigate this hypothesis, we set up a study to determine tumor volume variability in similarly staged tumors of the head and neck. In this retrospective study, we have investigated the volumes of T3-staged tumors. With endoscopy, as well as with CT, this stage produces a well recognizable tumor bulk that we were able to use for volume analysis.

MATERIALS AND METHODS

Patient material consisted of 84 patients that were seen in our hospital between 1990 and 1995 with previously untreated head and neck carcinoma. All patients

were clinically staged T3 according to TNM criteria.[9] Staging included complete history, physical examination, and direct examination under general anesthesia. Thirteen patients had to be excluded because no pretreatment CT scan was available. The remaining 71 patients underwent pretreatment CT scanning as part of the staging procedure.

Computerized tomographic scans were performed on a Somatom Plus CT-scanner (Siemens, Erlangen) using the larynx protocol; 120 kV (peak), 290 mA, and 2 seconds scan time. High-dose intravenous. contrast was given as a combination of a 50-mL bolus injection (flow rate 3.0 mL/s, delay 30 s), followed by infusion of 85 mL contrast material (flow rate 0.3 mL/s). Transverse sections were obtained from the mastoid tip to the clavicles. Either 5-mm consecutive sections, or 5-mm sections with a 2-mm increment were made.

To achieve reliable volume measurements we selected only those CT scans that were free of motion and/or dental artifacts and that displayed distinct tumor boundaries. To obtain a precise understanding of the local tumor extent, the CT scans were evaluated in combination with the clinical data on extension of the primary tumor obtained by endoscopy and the pathology report of the operation specimen, if available.

For the actual volume analysis we used the summation-of-areas technique, a method of volume calculation from sequential CT images. This method requires manual outlining of the lesion with a mouse on each tumor-containing CT section, which was done by the first author (F.A.P.) at the CT-scanner using the volume-measurement function, available on most scanners. The volume function on our CT scanner allows the definition of a range of CT density numbers that are automatically included in the volume analysis. Densities outside this range are excluded even when present in the outlined region of interest (ROI). In this manner, we could automatically exclude bone, air, and fat from the volume calculations which significantly simplified drawing of the individual ROI's (Figure 1). For every section the volume function calculates the volume in cubic centimeters within the ROI, taking into account selected density range, magnification factor, slice thickness, and increment. Individual slice volumes are added to the volume of the preceding sections. When the tumor is completely outlined on the sequential images, the end result is equal to the total tumor volume. No attempt was made to differentiate between tumor and surrounding edema.

Tumor volume differences of larynx and hypopharynx were tested for statistical significance (Wilcoxon two-sample test).

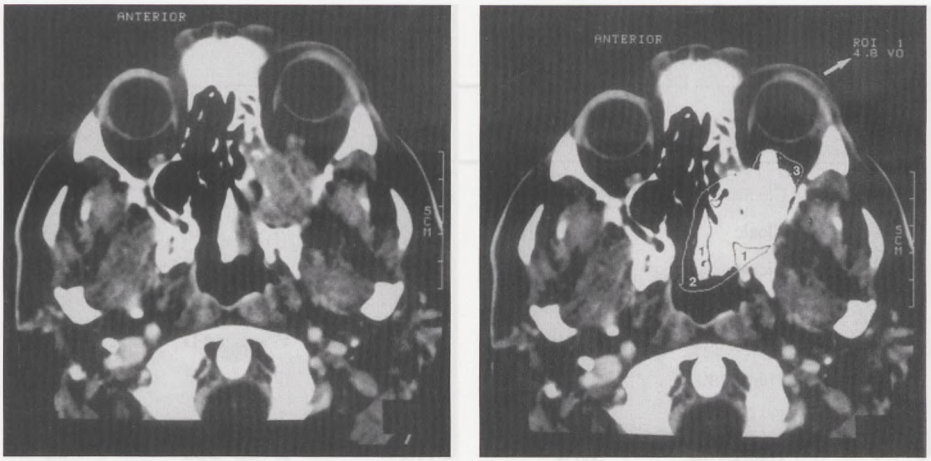

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FIGURE 1. CT axial section of a patient with ethmoidal sinus carcinoma. (**A**) Plain CT section showing carcinoma of the left ethmoid sinus, extending into the nasal cavity and invading the left orbit. (**B**) Tumor volume analysis using the volume measurement function. Automatic exclusion of bone-, air-, and fat-densities simplifies outlining the tumor. General outlining of tumor boundaries suffices. Only the bright pixels are included in the volume analysis. 1: automatic exclusion of bone (nasal septum, and part of left pterygoid plates). 2: automatic exclusion of air in nasal cavity. 3: automatic exclusion of orbital fat. The calculated volume in this section is 4.8 cm^3 (straight arrow). Note: this patient was not included in the study, but selected to demonstrate the volume analysis technique.

RESULTS

Pretreatment CT scans of 71 patients were available, of which we had to exclude 29. Reasons for exclusion were patient movement and/or swallowing artifacts (n = 4), dental artifacts (n = 9), and indistinct tumor boundaries (n = 16). Consequently, acceptable-quality pretreatment CT scans were available in 42 patients with carcinoma of the following primary sites: larynx (n = 12), oropharynx (n = 13), hypopharynx (n = 10), nasopharynx (n = 3), and maxillary sinus (n = 4). There were 38 men and 4 women, with a mean age of 63.5 years (range 30 to 82 years). Most tumors in these patients were irregularly shaped, as is a common observation in the head and neck. The tumor boundaries, however, were sharply defined, either by contrast enhancement or by natural contrast between soft-tissue (tumor) density and surrounding bone-, air- and fat-densities. In many cases, the endoscopy and/or pathology reports were helpful in further defining tumor extent.

In 12 patients with laryngeal carcinoma, tumor volumes between 1.6 and 17.0 cm^3 were found (median 3.7 cm^3). In the group of 13 patients with oropharyngeal cancer, we found tumor volumes between 10.0 and 41.2 cm^3 (median 18.3 cm^3). In

TABLE 1

T3 Larynx carcinoma ($n = 12$)

Patient	Site	Clinical stage	Treatment*	Follow-Up ‡	Volume (cm^3)
1	Glottic	T3N0	RT	42 mo DOC	1.6
2	Glottic	T3N0	RT	4 mo LFU	2.4
3	Glottic	T3N0	RT	17 mo NED	2.8
4	Transglottic	T3N0	S + RT	26 mo DOD	1.7
5	Transglottic	T3N0	RT + S	45 mo NED	3.3
6	Transglottic	T3N0	NT	17 mo DOC	3.6
7	Transglottic	T3N0	RT	30 mo NED	3.7
8	Transglottic	T3N2	S + RT	18 mo DOD	8.5
9	Supraglottic	T3N0	S + RT	16 mo NED	6.3
10	Supraglottic	T3N2	S + RT	18 mo DOD	8.0
11	Supraglottic	T3N3	S + RT	40 mo NED	13.7
12	Supraglottic	T3N2	RT	11 mo DOD	17.0

** NT: no treatment; RT: radiotherapy; S: Surgery.*

‡ DOC: died of other causes; DOD: died of disease; LFU: lost to follow-up; mo: months; NED: no evidence of disease.

10 patients with hypopharyngeal carcinoma, we found tumor volumes between 8.9 and 67.8 cm^3 (median 17.4 cm^3). Individual data of these three groups are given in Tables 1-3. Tumor volumes of larynx and hypopharynx showed a significant difference ($p = 0.0001$). There were three patients with carcinoma of the nasopharynx. Tumor volumes were, respectively, 3.7 cm^3, 25.3 cm^3, and 30.1 cm^3 (mean 19.7 cm^3). They were all treated with definitive radiotherapy (RT) and have no evidence of recurrence at the primary site (follow-up > 2.5 years). In four patients with maxillary sinus carcinoma volumes were: 56.0 cm^3, 62.7 cm^3, 77.3 cm^3, and 103.1 cm^3 (mean 74.8 cm^3). These were treated with RT or a combination of chemotherapy and irradiation. One patient with a 56.0- cm^3 tumor died of other causes within one year. The other three died of disease at respectively 12, 15,. and 18 months posttreatment.

DISCUSSION

In this study, we described a method of calculating tumor volume from the pretreatment CT scans of patients with T3 head and neck tumors. We have used

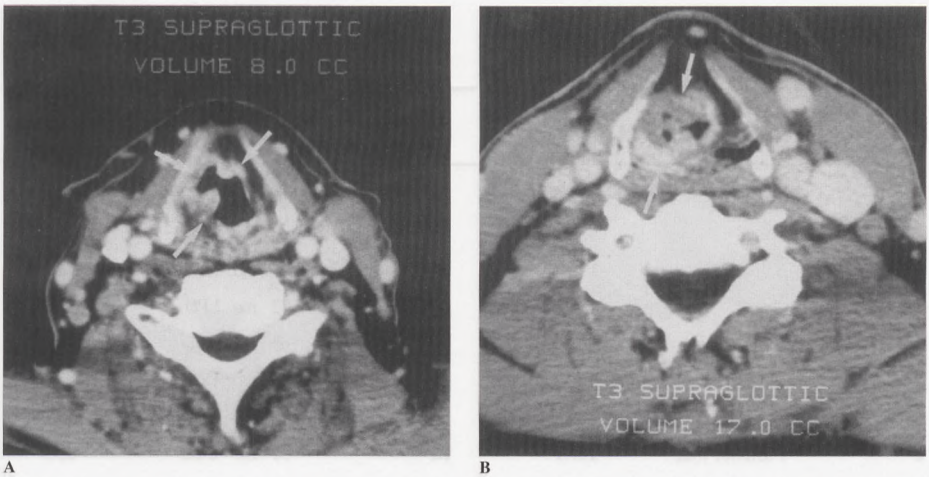

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FIGURE 2. CT axial sections of two different patients with T3 supraglottic larynx carcinoma showing difference in tumor volume of > 100%. (**A**) Superficial semicircular tumor (straight arrows); total volume = 8.0 cm^3. (**B**) Bulky tumor (straight arrows); total volume = 17.0 cm^3.

the summation-of-areas technique.[10] Various studies showed that the mean percentage errors of volume calculations using this technique were within a range of 5-10% when compared with volumes determined by water displacement[10-12], indicating that this technique can be used for reliable tumor volume measurements. The reproducibility of volume measurements performed on our own scanner was even better than 5%.

In each investigated subsite we found that tumor volume variability was striking, with variations exceeding 100% (Figures 2-4). The explanation for these large differences is that the TNM definitions of T3 head and neck carcinoma are based exclusively on unidimensional extension or vocal cord fixation. In our opinion, these parameters by no means represent the underlying tumor mass.

Detailed knowledge of tumor volume has clinical relevance, because many authors have demonstrated a positive correlation between tumor volume and local tumor control and survival rates for head and neck tumors at different subsites. Most of these studies are restricted to the larynx[3,4,7,8], and oropharynx.[5,6] *p*-Values range from 0.05 to 0.4. Detailed CT volumetric studies of head and neck tumors are limited in number, especially of one T-stage.

In four such studies on laryngeal carcinoma the authors tried to find cut-off points for tumor volumes, to select patients for treatment with radiotherapy alone, as opposed to laryngectomy.[3,7,8,13] Gilbert et al.[8] described 37 patients with relatively

TABLE 2

T3 Oropharynx carcinoma ($n = 13$)

Patient	Site	Clinical stage	Treatment*	Follow-Up ‡	Volume (cm^3)
1	Tonsil	T3N0	S + RT	16 mo DOD	10.0
2	Tonsil	T3N0	S + RT	27 mo NED	10.9
3	Vallecula	T3N2	S + RT	23 mo NED	12.5
4	Tonsil	T3N2	S	2 mo LFU	17.7
5	Soft palate	T3N2	S + RT	63 mo NED	17.8
6	Posterior wall	T3N0	RT	9 mo DOD	18.0
7	Tonsil	T3N2	S + RT	10 mo DOC	18.3
8	Posterior wall	T3N1	RT	38 mo DOD	20.0
9	Posterior wall	T3N2	S + RT	20 mo DOD	25.6
10	Tonsil	T3N2	RT	19 mo DOD	33.9
11	Tonsil	T3N2	RT	11 mo DOD	34.2
12	Tonsil	T3N2	RT	72 mo NED	35.7
13	Tonsil	T3N1	RT	27 mo NED	41.2

** RT: radiotherapy; S: Surgery.*

‡ DOC: died of other causes; DOD: died of disease; LFU: lost to follow-up; mo: months; NED: no evidence of disease.

advanced supraglottic and glottic primary tumors (T2 or greater) and showed that the tumor volume determined from pretreatment CT scans was the most important predictor for a successful outcome with definitive RT. In this study there was a subset of 10 patients with T3 laryngeal carcinoma. The volume analyses of these tumors were categorized in volume subgroups, but the overall range was comparable to our data. The study by Freeman et al.[7] on T1-T4 supraglottic larynx carcinoma showed that tumor volume, as measured on CT, could stratify patients into groups very likely and those much less likely to be controlled at the primary site with definitive RT. In a follow up study of 63 patients by Mancuso et al.[13], this trend was confirmed; 89% of primary lesions with a tumor volume under 6 cm^3 were controlled with laryngeal preservation by definitive RT, while only 40% of patients with tumor volumes over 6 cm^3 were controlled and retained their larynges ($p = 0.00004$). Lee and associates[3] studied 29 patients with T3 glottic larynx carcinoma. They found that both tumor volume and tumor involvement of specific sites within the larynx proved to be prognostic variables with an impact on local control.

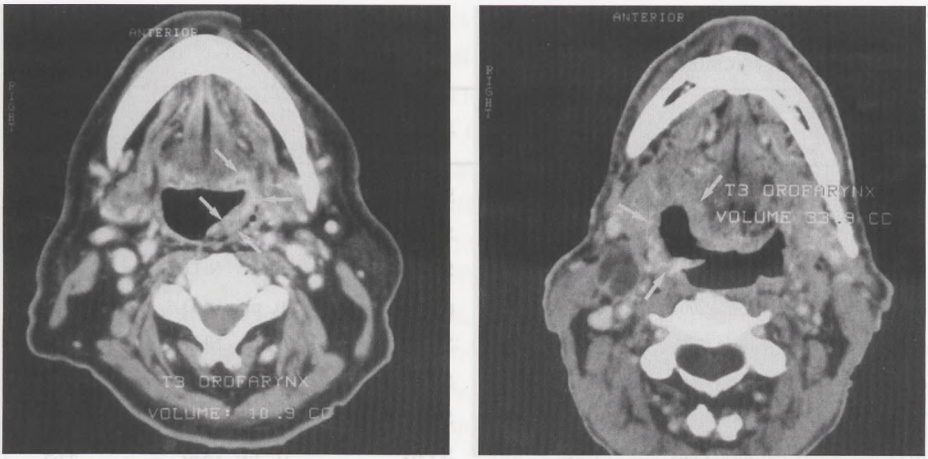

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FIGURE 3. CT axial sections of two different patients with T3 oropharyngeal (tonsillar) carcinoma showing difference in tumor volume of > 100%. (**A**) Relatively small mass, protruding into the oropharynx (straight arrows); total volume = 10.9 cm^3. (**B**) Large tumor process involving the right oropharynx (straight arrows); total volume = 33.9 cm^3.

Our institution is mainly surgically driven; therefore, our data on local control by RT alone are scarce. A definitive statistical analysis of tumor volume versus local control, as presented in the studies mentioned before, was not possible in our patient group (Tables 1-3).

In our study, we have included volume measurements on all major head and neck sites. However, we feel that volume data will be most useful in those sites that are not readily accessible for clinical and/or endoscopic inspection. This applies mainly to the larynx and hypopharynx. It is an interesting observation that tumor volumes of T3 larynx and hypopharynx carcinoma showed a highly significant difference ($p = 0.0001$), although the main criterion for defining T3-stage in these subsites is the same, ie, vocal cord fixation. It may be important to realize that this large difference in tumor volume by itself already contributes to the well-known difference in prognosis between these similarly staged tumors.

In nasopharynx carcinoma the clinical impact of detailed volume measurements seem somewhat less important. Olmi et al[14] reported that CT-derived information modified T-stage frequently for this site. However, in the second part of this report, Cellai et al[15] showed that T stage in itself has only a minor influence on prognosis in nasopharyngeal cancer. This is in concert with our own findings. The three patients with nasopharyngeal carcinoma showed large variation in volume (3.7-30.1 cm^3), but all were controlled at the primary site.

TABLE 3

T3 Hypopharynx carcinoma ($n = 10$)

Patient	Site	Clinical stage	Treatment*	Follow-Up ‡	Volume (cm^3)
1	Pyriform sinus	T3N0	S	24 mo NED	8.9
2	Pyriform sinus	T3N1	S + RT	17 mo DOD	15.8
3	Pyriform sinus	T3N1	S +RT	16 mo NED	17.0
4	Pyriform sinus	T3N3	pall RT	26 mo DOD	17.2
5	Pyriform sinus	T3N0	S + RT	36 mo NED	17.4
6	Pyriform sinus	T3N1	S + RT	66 mo NED	17.4
7	Pyriform sinus	T3N1	S +RT	16 mo NED	28.5
8	Pyriform sinus	T3N2	S + RT	11 mo DOD	44.4
9	Pyriform sinus	T3N3	RT	3 mo DOD	54.0
10	Pyriform sinus	T3N2	S + RT	33 mo NED	67.8

** Pall: palliative; RT: radiotherapy; S: Surgery.*
‡ DOD: died of disease; mo: months; NED: no evidence of disease.

In oropharyngeal carcinoma, the oral tongue and tong base can be readily inspected, and a "clinical"-volume estimate can be made. This is in concert with our observation that tumor volume variability is more outspoken in those subsites (e.g. larynx, hypopharynx) that are defined by anatomical extent than, for instance, oropharynx carcinoma, which is defined by maximum diameter. In our data, there is a much larger range of tumor volumes in larynx and hypopharynx carcinoma (tenfold and sevenfold, respectively) compared with oropharynx carcinoma, which showed a four times difference between smallest and largest volumes measured.

Our observations correspond with those of Johnson et al.[2] in demonstrating again that the current TNM staging system fails to define the true three-dimensional bulk of tumors in the head and neck, especially within a given stage. Because the TNM staging system is, amongst others, developed for prognostic purposes, it may be worthwhile to add tumor volume data to the existing TNM classification. This would mean a further refinement of the staging system. Several authors have made suggestions to modify the T-classification of the TNM system by incorporating CT-derived information and tumor volume data.[2,16-17] We agree with these authors, because we think that volume data may help to identify prognostic differences, especially within the same stage. However, this would mean that volume analyses should be performed on a routine basis. Regarding this aspect, we need to make several comments.

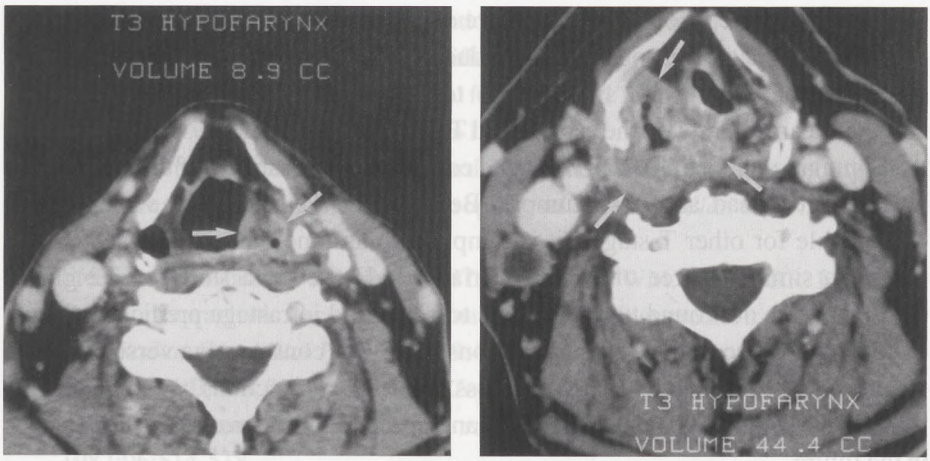

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FIGURE 4. CT axial sections of two different patients with T3 hypopharyngeal (pyriform sinus) carcinoma showing difference in tumor volume of > 100%. (**A**) Small mass still confined to pyriform sinus (straight arrow); total volume = 8.9 cm^3. (**B**) Large tumor bulk (straight arrows); total volume = 44.4 cm^3.

The technique required to measure tumor volumes is relatively simple, providing that good quality images are available. A practical problem in our study was that the volume analysis itself is time-consuming. Outlining the tumor and data processing require about 20 minutes for the Somatom Plus scanner. Most current CT scanners have the equivalent of the volume function and can perform this simple task much faster (±5 minutes), especially if an independent workstation is available.

The 40% exclusion rate of CT scans in our study is very high. The reasons for this are several. In this retrospective study, we excluded 13 scans that were adequate for diagnostic purposes on the basis of motion and/or dental artifacts. In the majority of these cases, there were only one or two sections with these artifacts. In a prospective setting, especially if volume is an issue, these sections could have been repeated directly after the scan. This would have eliminated the motion artifacts. By adjusting the plane of section, it is possible to minimize or avoid dental-filling artifacts in the majority of cases. Sixteen tumors were excluded because of indistinct boundaries. Many of these had only partially indistinct boundaries that, for practical purposes, could have been measured. For these cases, it would have been necessary to study the interobserver variability, which was not evaluated in this study. Indistinct tumor boundaries on CT may be clearly depicted on MRI (magnetic resonance imaging). A disadvantage of MRI is that it produces less bony detail, especially if early bone erosion is an issue. In such cases automatic three-dimensional correlation of CT/MRI studies, using matching techniques, can become very important.[18]

Based on these recommendations, we expect that the number of exclusions for volume analysis can be considerably reduced. With state-of-the-art technique, the exclusion rate should not succeed 5% to 10%. In the remaining patients, the clinicians can still rely on the established TNM criteria.

Summarizing, in this study we found considerable variability of tumor volumes in T3-staged head and neck tumors. Because the TNM system variables are comparable for other T-stages, it is tempting to assume that other T-stages will display a similar degree of volume variability. However, a study on T2 glottic carcinoma has not found tumor volume to be a good intrastage predictor of local control.[19] Because of the treatment options involved (conservative versus surgery, frequently associated with permanent loss of laryngeal function), we think that T3 is the "key-stage" for volume data to have an impact on patient-management decisions in the future.

CONCLUSION

In this study, we have found considerable variability of tumor volumes in T3-staged head and neck tumors. This confirmed that the current TNM system is unable to group tumors with the same size into the same (T3) stage group. Based on the literature to date on the significance of tumor volume with regard to local control and survival, we think that tumor volume analyses, as have been described in this report, can be a useful parameter in future research of head and neck tumors. We argue in favor of incorporation of tumor volume data leading to a further refinement of the TNM classification.

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CHAPTER 3

Can pretreatment computed tomography predict local control in T3 squamous cell carcinoma of the glottic larynx treated with definitive radiotherapy ?

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ABSTRACT

Purpose

To determine if pretreatment computed tomography (CT) can predict local control in T3 squamous cell carcinoma of the glottic larynx treated with definitive radiotherapy (RT).

Materials and Methods

Forty-two patients with previously untreated T3 squamous cell carcinoma of the glottic larynx were treated for cure with RT alone; all had a minimum 2-year follow-up. Tumor volumes and extent were determined by consensus of two head and neck radiologists on pretreatment CT studies. A tumor score was calculated and assigned to each primary lesion depending on the extent of laryngeal spread. Sclerosis of any laryngeal cartilage was recorded. The specific CT parameters assessed were correlated with local control.

Results

Tumor volume was a significant predictor of local control. For tumors measuring < 3.5 cm^3 local control was achieved in 22 of 26 patients (85%), whereas for tumors ≥ 3.5 cm^3 local control was achieved in 4 of 16 patients (25%) ($p = 0.0002$). Sensitivity and specificity using this cutpoint were 85% and 75%, respectively. Tumor score as a measure of anatomic extent was also found to be a significant predictor of local control. The local control rate for tumors assigned a low tumor score (≤ 5) was 78% (21 of 27) compared to 33% (5 of 15) for tumors assigned a high tumor score (6, 7, or 8) ($p = 0.008$). A significant decrease in the local control rate was observed for cancers involving the paraglottic space at the false vocal cord level (14 of 16 [88%] vs. 12 of 26 (46%]) ($p = 0.010$), cancers involving the face of the arytenoid (15 of 18 [83%] vs. 11 of 24 [46%]) ($p = 0.024$), and tumors involving the interarytenoid region (25 of 36 [69%] vs. 1 of 6 [17%]) ($p = 0.020$). There were 12 patients with sclerosis of both the ipsilateral arytenoid and the adjacent cricoid cartilage. These patients showed a significant decrease in local control (4 of 12 [33%]).

Conclusion

Pretreatment CT can stratify patients with T3 glottic carcinoma into groups more or less likely to be locally controlled with definitive RT. The local control rate for these tumors can be improved using a CT-based tumor profile; the ideal CT profile for a radiocurable T3 glottic larynx carcinoma is volume < 3.5 cm^3 and no or single laryngeal cartilage sclerosis.

INTRODUCTION

The treatment of T3 glottic carcinoma varies among institutions. The treatment options include total laryngectomy or extended hemilaryngectomy with or without adjuvant radiotherapy (RT) and RT alone with laryngectomy reserved for local recurrence.[1-4] The role of adjuvant chemotherapy in laryngeal preservation has also been investigated.[5,6]

Radiation therapy has proven to be an effective modality with rates of local-regional control, survival, and severe complications that are similar to those obtained with surgery alone or surgery combined with adjuvant irradiation.[4,7] In contrast to radical surgery, RT provides a treatment alternative which allows for preservation of laryngeal function.

Conservation surgery, in the form of extended hemilaryngectomy offers the same option of preserving laryngeal function with local-regional control rates that are comparable to, if not slightly better than, those obtained with RT alone. However, most patients have lesions that are too advanced at the time of presentation to be suitable for this type of surgery.

The local-regional control rate for T3 squamous cell carcinoma of the glottic larynx treated with definitive RT at our institution over a 23-year period reviewed in 1992 was 62%.[4] Other centers have reported similar results with RT alone.[8-11] Stratification of patients into high vs. low risk for failure at the primary site with definitive RT might improve the current local control rates and reduce the morbidity of treatment by triaging some patients to a perhaps more appropriate surgical procedure, since salvage surgery after recurrence is associated with a high risk of complication.[4,12] Those high-risk patients who elect to proceed with RT may require a more intense clinical surveillance of the primary site after treatment, including periodic imaging studies. Salvage surgery, if required, might then be instituted earlier in hopes of improving the overall local control rate.

The selection criteria for treatment with primary irradiation at our institution were historically based on clinical examination at the time of diagnosis and patient willingness to return for frequent follow-up visits. More recently CT has been shown to be potentially useful in this selection process.[13]

This study updates the previous report from our institution which identified those patients with T3 glottic carcinomas who had a higher likelihood of local control based on pretreatment tumor volume.[13] In that preliminary experience based on 18 patients, primary tumors with volumes of < 3.5 cm^3 had a 92% probability of local control while those lesions ≥ 3.5 cm^3 had a 33% control rate ($p = 0.02$).

The purpose of this study was to determine if CT volumetric analysis and/or a tumor score (based on the involvement of specific anatomic sites within the larynx) can be used to predict the likelihood of local control, with preservation of laryngeal function, in patients with a T3 carcinoma of the glottic larynx treated with definitive RT. The impact of sclerosis of adjacent laryngeal cartilages on radiocurability was also analyzed, since this has been shown to be a sign suggesting the presence of microscopic cartilage invasion.[14-16]

These variables, if significant, could be combined to create a pretreatment CT profile for T3 glottic carcinomas that stratifies patients into groups very likely (favorable) and those much less likely (unfavorable) to be controlled at the primary site with definitive RT. This CT profile can then be integrated with the traditional clinical considerations used to recommend treatment options to these patients.

MATERIALS AND METHODS

Forty-four patients with T3 squamous cell carcinoma of the glottic larynx who were treated with definitive RT from 1980 to 1993 underwent clinical staging and pretreatment contrast-enhanced CT. Patients were followed for a minimum of two years (median: 4 years, 3 months; range: 4 months to 14 years) after the completion of therapy, or until local recurrence. Patients were staged according to the 1988 recommendations of the American Joint Committee on Cancer.[17]

All patients were treated with 6,750 - 7,920 cGy via once-daily (n = 4) or twice-daily (n = 40) continuous-course irradiation. In some patients this was followed by a planned neck dissection. The treatment techniques have been described previously.[4,18]

Each patient underwent pretreatment, contrast-enhanced CT of the head and neck with 3-5-mm-thick contiguous sections. After 1986, all studies from this institution were done with contiguous 3-mm sections, field of view (FOV) = 12-18 cm, a 512 x 512 mm matrix, and the plane of section parallel to the true vocal cords.[19] These were then filmed in two different window settings; one suitable for evaluation of soft tissue, the other for evaluation of cartilage. All pretreatment studies were retrospectively reviewed by two of the authors (A.A.M, F.A.P.) who were unaware of patient outcomes. The tumor volumes and anatomic spread pattern of the tumor as defined by involvement at specific sites were recorded by consensus reached by the two reviewers for each patient.

The anatomic sites evaluated included (a) the anterior commissure, (b) contralateral true vocal cord, (c) face of the ipsilateral arytenoid, (d) interarytenoid region, (e) ipsilateral ventricle, (f) the paraglottic space at the true vocal cord level, (g) the paraglottic space at the false vocal cord level, and (h) the subglottic region.

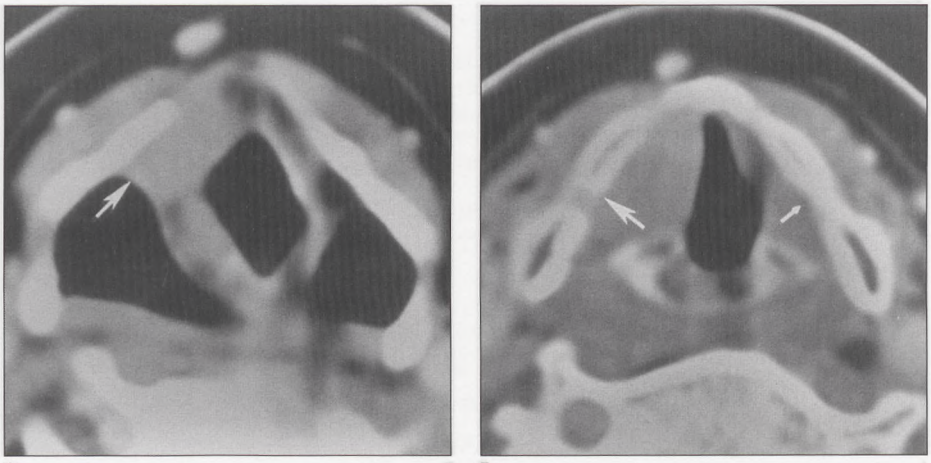

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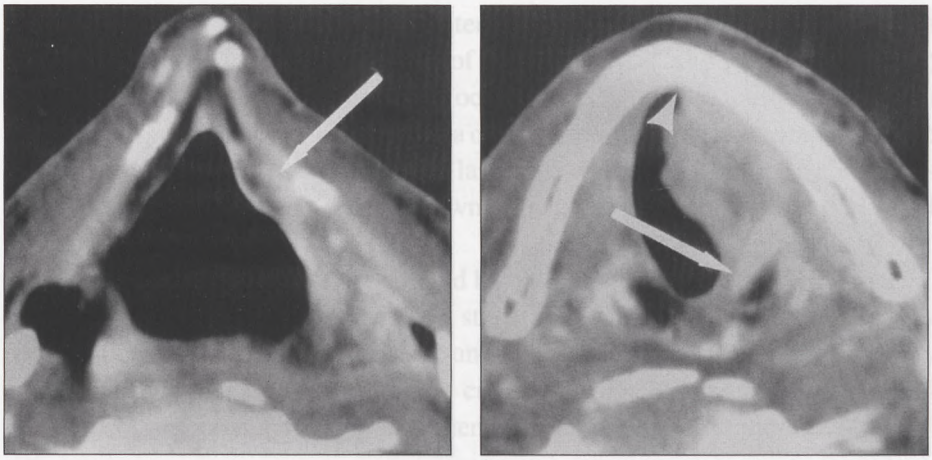
FIGURE 1. CT scan of a patient with a 2.1-cm³ carcinoma of the right true vocal cord and a tumor score of 4. (**A**) Image just above the false cord level demonstrates involvement of the right aryepiglottic fold and obliteration of the paraglottic space (arrow). (**B**) Image at the true vocal cord level demonstrates involvement of the entire cord which is in paramedian position. The ipsilateral paraglottic space is obliterated (large arrow), compared to the contralateral paraglottic space (small arrow) without anterior commissure involvement or posterior spread. Subglottic extension (not shown) was also present. The patient is alive without evidence of disease 31 months after the completion of radiotherapy.

A total score was assigned to each tumor score that was equal to the number of anatomic sites involved, based on the pretreatment CT scan (Figures 1-3). For example, a lesion involving the ventricle, paraglottic space both at the false and true vocal cord level and the subglottic region had a tumor score of 4. Tumor scores ranged from 1 to 8.

To determine tumor volume, the primary lesion was outlined on each CT slice that contained tumor. No attempt was made to differentiate tumor from related edema. The volume of the entire true vocal cord (TVC) was always included, since tumor density cannot be reliably differentiated from the muscle density of the TVC. Each study was evaluated, and when necessary, corrected for errors related to patient movement, respiratory misregistration, or technologist error in selection of slice location. Tumor outlines were then transferred into a treatment-planning computer using a digitizer. After accounting for the magnification factor of the scan and CT slice thickness, the computer generated a tumor volume measured in cubic centimeters for each primary lesion.



A B

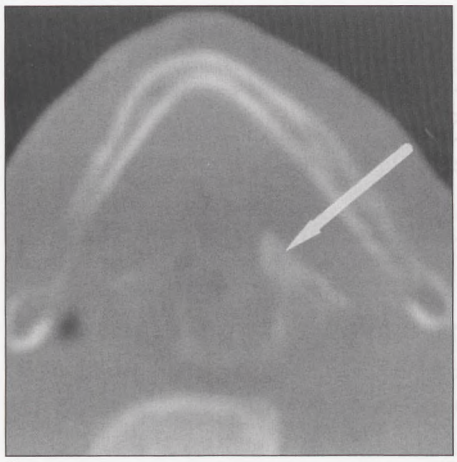
FIGURE 2. CT scan of a patient with a 4.3-cm³ carcinoma of the left true vocal cord and a tumor score of 6. (**A**) Image at the false cord level demonstrates involvement of the left aryepiglottic fold and obliteration of the paraglottic space (arrow). (**B**) Image at the true vocal cord level demonstrates a bulky lesion that involves the entire cord, extends just onto the anterior commissure (arrowhead) as well as the face of the ipsilateral arytenoid (arrow) and obliterates the paraglottic space.

Presence or absence of sclerosis and/or possible focal erosion of any laryngeal cartilage adjacent to tumor was recorded. Patients with through-and-through evidence of cartilage invasion (e.g., tumor on both sides of the thyroid cartilage) were considered to have T4 lesions and were not included.

Two patients who died of intercurrent disease < 2 years from treatment were excluded even though they were continuously disease-free at the primary site. After these exclusions, 42 patients remained and are the subjects of this report. Major treatment complications included laryngeal necrosis and/or edema which resulted in complete, permanent loss of laryngeal function. Ultimately, these patients were permanently tracheostomy-dependent or underwent laryngectomy. Mild laryngeal pain or hoarseness in a patient with an otherwise normally functioning larynx was classified as a minor complication and not considered in the outcome analysis. The end point for all analyses was local control or local recurrence after RT alone, without a major complication.

Statistical methods

Local control rates were compared between patient strata defined by the various pretreatment CT parameters using Fisher's exact test. Each observed tumor score



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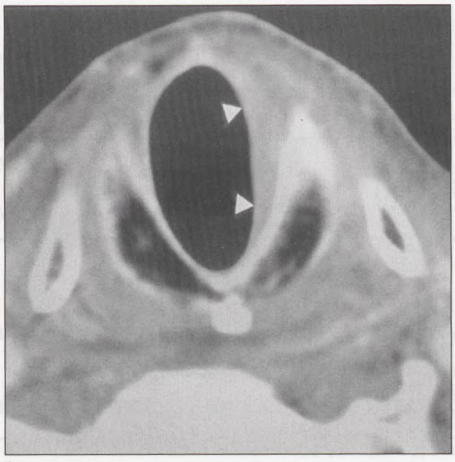

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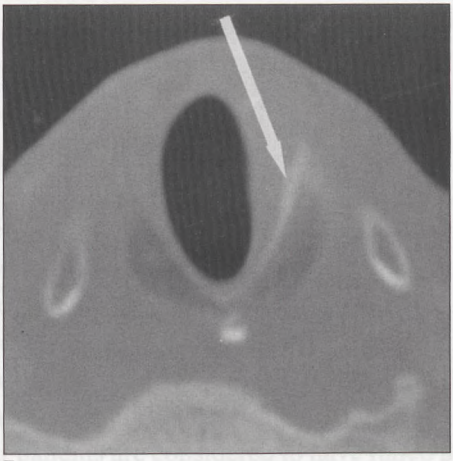

E

FIGURE 2 CONTINUED. (**C**) Bone detail image at the same level as Fig. 2b shows associated sclerosis of the arytenoid cartilage (arrow). (**D**) Image at the subglottic level showing continued tumor spread on the left side (arrowheads). (**E**) Bone detail image at the same level as Fig. 2d demonstrates sclerosis of the adjacent part of the cricoid cartilage (arrow). The patient experienced a primary failure 4 months after the completion of radiotherapy; a salvage total laryngectomy was performed and the patient is alive without evidence of disease 27 months after the operation.

and volume was also used as a cutpoint, to define low-risk and high-risk patient strata, which were then compared in a similar manner. Sensitivity and specificity for local control were computed for each cutpoint, and optimal tumor score and volume cutpoints were then determined based on statistical significance and maximum difference in local control rates between cutpoint-defined strata. An exact test for linear trend in ordered proportions available in the EGRET epidemiological statistics software package (Statistics and Epidemiology Research Corporation, Seattle WA) was used to test for the presence of a linear trend in local control rates as a function of number of laryngeal cartilages involved or as a function of ordered risk groups defined simultaneously by cartilage involvement and tumor volume.

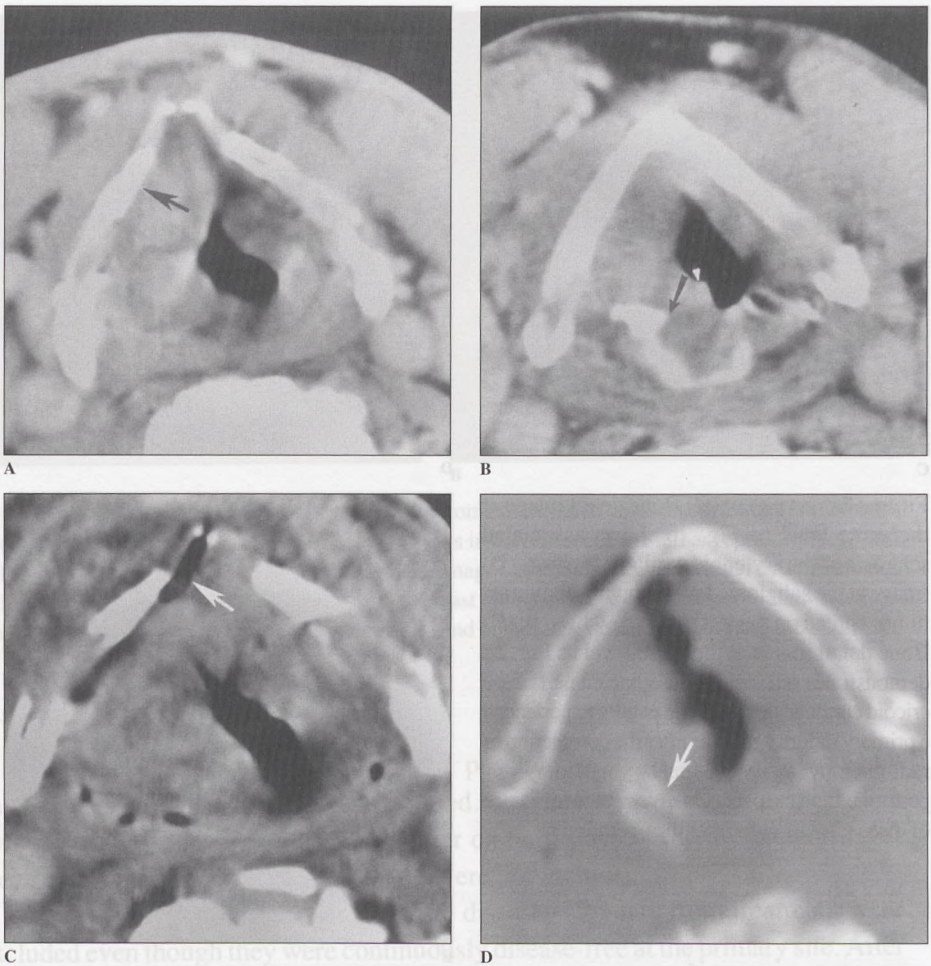

FIGURE 3. CT scan of a patient with a 7.5-cm³ carcinoma of the right true vocal cord and a tumor score of 8. (**A**) Demonstrates involvement of the false vocal cord and obliteration of the paraglottic space (arrow). (**B**) The entire true vocal cord is thickened and tumor extends to the anterior commissure and the contralateral true vocal cord as well as posteriorly to involve the arytenoid face (arrow) and interarytenoid region (arrowhead). There is associated sclerosis of the ipsilateral arytenoid cartilage. Subglottic extension was also present (not pictured). Uneven ossification of the thyroid cartilage on both sides is considered a normal variant. (**C**) Follow-up CT at 11 months post-RT, when the patient developed breathing difficulties, shows gross soft-tissue swelling both endolaryngeal at the supraglottic level as well as in the neck. There is a small amount of air in the paraglottic space anteriorly (arrow). (**D**) Bone detail image at the undersurface of the true vocal cords shows air outside the larynx which is strongly suggestive of chondronecrosis and/or superimposed infection. Local recurrence cannot be excluded. Note associated sclerosis of the cricoid cartilage (arrow), which was also present on the pre-RT CT scan. The patient underwent total laryngectomy 13 months post RT. No tumor was found in the specimen.

TABLE 1

Local control by tumor volume on pretreatment CT ($n = 42$)

Tumor volume	Local control	
< 3.5 cm^3	22/26 (85%)	$p = 0.0002$
≥ 3.5 cm^3	4/16 (25%)	

Logistic regression was used to determine if total tumor volume was linearly associated with the log odds of local control, and also to determine if any simultaneous combination of pretreatment CT parameters provided significant and independent information regarding the probability of local control. The Spearman rank correlation coefficient was used to assess correlation between tumor volume and tumor score.

RESULTS

Forty-two patients were evaluated for local control. Of these 42, 30 patients (71%) remained continuously free of disease at the primary site after RT alone, while 12 patients (29%) developed a local recurrence. Four patients (9.5%) who were controlled at the primary site underwent total laryngectomy for suspected recurrence and/or laryngeal necrosis, and no tumor was found in the specimen. Three of these patients with laryngeal necrosis and tumor volumes of 3.0, 7.5 (Figure 3b,d) and 7.9 cm^3 respectively, had sclerosis of the ipsilateral arytenoid cartilage and the cricoid. The other patient with a 2.2-cm^3 tumor had no laryngeal cartilage sclerosis. In all of the following analyses, these four patients are considered to have failed at the primary site (i.e., lost laryngeal function permanently). Thus, 26 of 42 patients (62%) who were treated with definitive RT were controlled at the primary site with preservation of laryngeal function, while 16 of 42 (38%) lost laryngeal function due to either local failure ($n = 12$) or a treatment-related complication ($n = 4$).

There was a significant relationship between tumor volume and the rate of local control (Figure 4). Those primary lesions in which the tumor volume was < 3.5 cm^3 were controlled in 22 of 26 patients (85%), compared with 4 of 16 (25%) for lesions ≥ 3.5 cm^3 ($p = 0.0002$) (Table 1). The sensitivity and specificity for local control using the 3.5-cm^3 tumor volume cutpoint were 85% and 75%, respectively. Tumor volume over the entire range of observed values was also a significant linear predictor of local control ($p = 0.0004$). Figure 4 illustrates the predicted probability

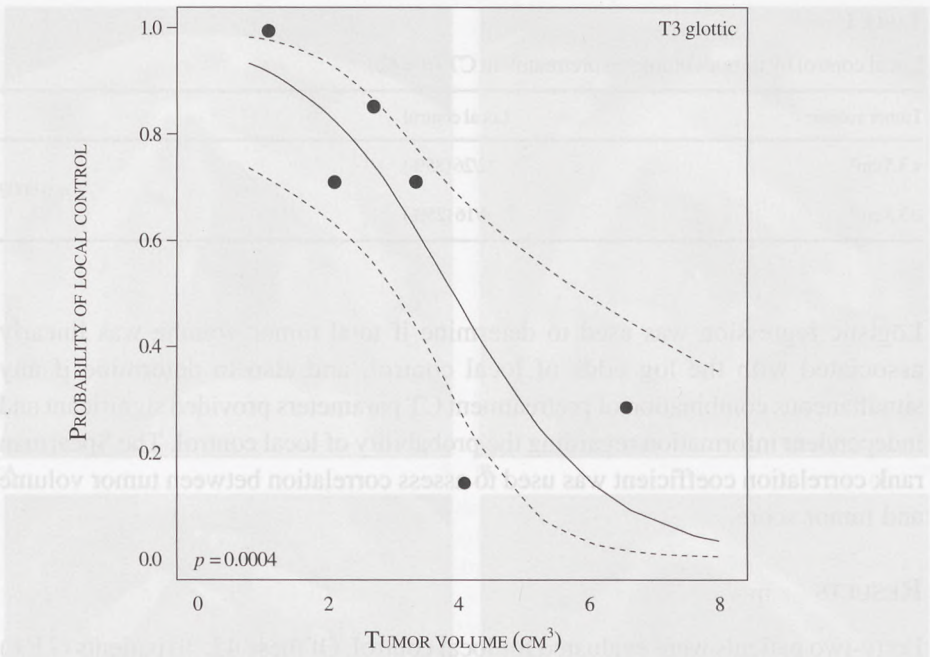

FIGURE 4. Predicted probabilities for local control as a function of tumor volume for 42 patients with T3 glottic larynx carcinoma. Solid lines show predicted probabilities for local control as a function of pretreatment CT; dashed lines show 95% confidence bands. Predicted probabilities were estimated by modeling the log odds of local control as a linear function of tumor volume. Significance of the fitted model is indicated by the *p* value displayed in the plot. Individual points represent the proportion of patients who achieved local control in subgroups defined by ordered tumor volume intervals. Each point represents seven patients.

for local control as a function of tumor volume, along with observed proportions for local control among subgroups of patients ordered by observed volume intervals (n = 7 patients/subgroup).

The total tumor score assigned to each primary lesion was also significantly associated with the probability of local control. Primary lesions with a score of ≤ 5 had a local control rate of 75% (21 of 28), compared with 36% (5 of 14) for primary lesions assigned a score of 6, 7, or 8 ($p = 0.002$) (Table 2). The sensitivity and specificity for local control using the tumor score cutpoint of 6 were 81% and 64%, respectively. There was a moderate degree of positive correlation between tumor volume and tumor score (Spearman $R = 0.66$).

Local control rates after RT alone are shown in Table 3 as a function of involvement of various anatomic subsites within the larynx, as determined by

TABLE 2

Local control by tumor score on pretreatment CT ($n = 42$)

Tumor score	Local control	
≤5	21/28 (75%)	$p = 0.002$
>5	5/14 (36%)	

pretreatment CT. There was a significant decrease in local control rates for tumors that involved the paraglottic space at the level of the false vocal cord ($p = 0.010$) (Figure 2a) and for tumors involving the face of the arytenoid ($p = 0.024$) (Figure 2b). Presence of tumor in the interarytenoid region was also significant for decrease in local control ($p = 0.020$) (Figure 3b). The combination of involvement of the paraglottic space from the false cord level to the subglottic region (Figure 2a,b,d) proved to be marginally significant ($p = 0.050$). No other specific site or pattern proved to be a significant individual determinant of local control.

There were 26 patients with sclerosis of one or more of the arytenoid and cricoid cartilages. The overall control rate for tumors associated with sclerosis was 54% (14 of 26). This did not significantly differ from the local control rate of 75% (12 of 16) observed for patients without cartilage sclerosis ($p = 0.206$). There were 14 patients with sclerosis of a single laryngeal cartilage; in 12 patients the ipsilateral arytenoid was sclerotic, and in two only the cricoid was sclerotic. This group had a local control rate of 72% (10 of 14). There were 12 patients with sclerosis of both the ipsilateral arytenoid and the adjacent cricoid cartilage (Fig. 2c,e). In these patients the local control rate was 33% (4 of 12). The local control rate for patients with a single laryngeal cartilage involved did not differ significantly from the local control rate for patients with no cartilage involvement ($p = 0.825$). However, patients with both ipsilateral arytenoid and adjacent cricoid cartilage sclerosis had a significantly lower rate of local control than patients who had either a single cartilage or no cartilage involved ($p = 0.021$).

Two patients had radiographic evidence of focal cartilage erosion by tumor that was not appreciated prior to initial staging and treatment. One of these had erosion of the thyroid cartilage; this patient with a 7.9-cm^3 tumor developed chondronecrosis and underwent total laryngectomy with no tumor found in the specimen. The other patient, with a 3.7-cm^3 tumor, had erosion of the cricoid cartilage and failed locally. Both these patients, in addition to focal cartilage erosion, had also sclerosis of the ipsilateral arytenoid and the adjacent cricoid cartilage.

TABLE 3

Local control according to involvement of anatomic subsite on pretreatment CT ($n = 42$)

Site	Involved	Local control (%)	p Value
Anterior commissure	Yes	16/28 (57.1)	0.510
	No	10/14 (71.4)	
Contralateral true vocal cord	Yes	5/9 (55.6)	0.710
	No	21/33 (63.6)	
Face of arytenoid	Yes	11/24 (45.8)	0.024
	No	15/18 (83.3)	
Interarytenoid region	Yes	1/6 (16.7)	0.020
	No	25/36 (69.4)	
Ventricle	Yes	18/30 (60.0)	0.740
	No	8/12 (66.7)	
Paraglottic space at the true vocal cord level	Yes	21/37 (56.8)	0.140
	No	5/5 (100.0)	
Paraglottic space at the false vocal cord level	Yes	12/26 (46.2)	0.010
	No	14/16 (87.5)	
Subglottic region	Yes	24/39 (61.5)	0.999
	No	2/3 (66.7)	
Paraglottic space at the false vocal cord level + subglottic region	Yes	12/25 (48.0)	0.050
	No	14/17 (82.4)	

In an attempt to identify informative risk groups for local control on the basis of cartilage involvement and tumor volume, local rates for 3 patient strata were also compared (Table 4): The lowest-risk stratum included patients with tumor volumes < 3.5 cm^3 and ≤ 1 cartilage involved ($n = 21$); the moderate-risk stratum included patients with tumor volumes < 3.5 cm^3 and two cartilages involved, plus patients with tumor volumes ≥ 3.5 cm^3 and ≤ 1 cartilage involved ($n = 14$); the highest-risk stratum included patients with tumor volumes ≥ 3.5 cm^3 and 2 cartilages involved ($n = 7$). Local control rates differed significantly between the low-risk group (19 of 21 [90%]) and the moderate-risk group (6 of 14 [43%]) ($p = 0.006$) and between the low-risk group and the high-risk group (1 of 7 [14%]) ($p = 0.002$). Local control rates in the moderate-risk and high-risk groups did not differ significantly ($p = 0.337$). However, the linear trend in local control rates from the low-risk group to the moderate-risk group to the high-risk group was statistically significant ($p = 0.0005$).

Multiple logistic regression modeling indicated no combination of pretreatment CT parameters to be more significantly associated with the probability of local control than any parameter considered individually. Low or high tumor volume as defined by a cutpoint of 3.5 cm^3 was found overall to have the best sensitivity and

TABLE 4

CT risk profiles for patients with T3 glottic larynx carcinoma ($n = 42$)

Risk groups (for local recurrence)	Criteria	Nr of patients	Local Control
I Low risk ($n = 21$)	Volume < 3.5 cm³	13	
	No cartilage sclerosis		19/21 (90%)
	Volume < 3.5 cm³	8	
	Single cartilage sclerosis		
II Moderate risk ($n = 14$)	Volume < 3.5 cm³	5	
	> 1 cartilage sclerosis		
	Volume > 3.5 cm³	3	6/14 (43%)
	No cartilage sclerosis		
	Volume > 3.5 cm³	6	
	Single cartilage sclerosis		
III High risk ($n = 7$)*	Volume > 3.5 cm³	7	1/7 (14%)
	> 1 cartilage sclerosis		

** Two of these patients had focal cartilage erosion.*

specificity for local control. No other parameter provided additional significant information regarding the probability of local control when considered simultaneously with tumor volume.

DISCUSSION

The role of CT for imaging laryngeal and hypopharyngeal carcinomas has continued to evolve over the last 10 years as a result of technological advancements which have decreased scan acquisition time and otherwise improved our ability to obtain high resolution, thin-section (1-3-mm) images which permit a detailed evaluation of the laryngeal anatomy free of motion artifacts. Several studies have been performed correlating CT findings of laryngeal carcinoma with whole organ sections. These studies have shown that CT can accurately predict the site, size, and deep-spread patterns (except for disease limited to the mucosal lining) of laryngeal tumors.[14,15,20-24] Pretreatment imaging has been shown to improve the accuracy of staging and has become generally accepted as an adjunct to the physical examination for evaluation of laryngeal tumors at many institutions.[14,15,20-24]

This study updates and more than doubles the original experience from our institution concerning the value of CT in selecting patients for definitive RT of a T3 glottic larynx carcinoma. Our previous experience published by Lee et al.[13] showed tumor volume, as measured on CT, could stratify patients with T3 glottic squamous cell carcinoma into groups likely (92%) and much less likely (33%) to be controlled at the primary site; the volume cutpoint was 3.5 cm³.

Pretreatment CT volumetric analysis of the primary tumor has been shown to be a potentially effective predictor of local control in a variety of laryngeal tumors treated with RT alone.[25-28] Gilbert et al.[25] reported that tumor volumes determined from pretreatment CT scans were the most important predictor for a successful outcome with primary RT in a group of 37 patients with relatively locally advanced (≥ T2) supraglottic and glottic primary tumors; for patients who were cured by RT, the mean volume was 8.86 cm^3, with a standard deviation of 8.0 cm^3. In a similar study, Freeman et al.[27] were able to identify those patients with supraglottic carcinomas who had a higher likelihood of local control based on pretreatment tumor volume. Tumors with volumes of < 6 cm^3 had an 83% probability of local control, while those lesions with volumes ≥ 6 cm^3 had only a 46% control rate. In a follow-up study of 63 patients this trend was confirmed; 89% of primary tumors < 6 cm^3 were controlled with laryngeal preservation by definitive RT, while only 40% of patients with tumor volumes ≥ 6 cm^3 were controlled and retained their larynges ($p < 0.0001$).[28]

This study sought to establish a CT-based profile for T3 glottic larynx carcinoma that stratifies patients into groups favorable and less favorable to be controlled at the primary site with definitive RT. Variables that could be included in such a profile and that were tested in this study are tumor volume, tumor score, and sclerosis of the laryngeal cartilages.

Tumor volume

The local control rate for all tumors in the current study was 62%. This rate of local control is identical to the reported local control rate for the entire group of patients with T3 glottic cancer treated at the University of Florida, suggesting that the subset reported here is representative of the entire group.[4]

For tumors < 3.5 cm^3 the local control rate was 85% (22 of 26) (Figure 1). In contrast, 4 of 16 tumors ≥ 3.5 cm^3 were controlled at the primary site (local control rate 25%). This difference in likelihood of local control was significant, with $p = 0.0002$, and yielded a sensitivity of 85% and specificity of 75%; tumor volume thus appears to be a moderately good predictor of local control when using RT alone. The local control rate of 85% found in this study for low-volume T3 glottic tumors treated with RT is comparable, if not slightly better, than those obtained with surgery alone or combined with adjuvant irradiation at our institution.[4]

Pretreatment tumor volumes are likely to assume a role similar to that suggested for supraglottic carcinomas in helping to predict local control for T3 glottic larynx carcinomas.[27,28] This has important implications in the informed consent process,

since the patient can be presented with a more accurate assessment of the likelihood of local control with RT vs. conservation or radical surgery (Figure 4).

The volume cutpoint of 3.5 cm^3 in this study is considerably different from the critical volume (between 6 to 7 cm^3) suggested for supraglottic tumors. The reason for this difference is not completely understood. There might be biological factors involved, since the glottis and supraglottis have different embryological precursors. The reason for the lower critical volume for a glottic carcinoma might be anatomical and related to cricoarytenoid joint invasion. A glottic tumor is much more intimately related to the arytenoid, cricoid and thyroid cartilages and therefore may cause occult cartilage invasion, with its inherent decrease in radiocurability, at much lower volume than a supraglottic carcinoma. Cartilage-related risk factors are discussed in more detail subsequently.

Four tumors with volumes < 3.5 cm^3 failed locally. Two of these underwent total laryngectomy for suspected recurrence and/or laryngeal necrosis, and no tumor was found in the specimen. One of these relatively low-volume tumors produced sclerosis of the ipsilateral arytenoid and adjacent cricoid cartilage. The other patient had no cartilage sclerosis. Sclerosis of more than one laryngeal cartilage may be an additional risk factor for chondronecrosis; this will be discussed subsequently. The two other low-volume tumor recurred at the primary site; the cause of the failures was unclear. Perhaps these lesions were biologically aggressive or perhaps there were other unfavorable tumor-host interactions which are currently incompletely understood. One of these two patients with a low-volume tumor failure also had sclerosis of the arytenoid and cricoid cartilage raising the possibility that sclerosis of more than one cartilage may be a risk factor for local recurrence, in addition to radiation necrosis.

Four out of 16 patients (25%) with tumor volumes over 3.5 cm^3 were cured. Tumor volumes of these patients were 3.7, 4.2, 5.2 and 6.0 cm^3. Three of these patients had sclerosis of a single laryngeal cartilage (ipsilateral arytenoid: $n = 2$, cricoid: $n = 1$). One patient with a 6.0-cm^3 tumor had sclerosis of the ipsilateral arytenoid and adjacent cricoid cartilage. The control of these tumors agrees with the reported experience in supraglottic tumors that some high-volume lesions will be controlled at any laryngeal subsite.[28]

Tumor score

Like volume, tumor score with a cutpoint of 6 was able to stratify the patients into groups with relatively high vs. relatively low local rates control using RT. The sensitivity and specificity for local control were less than those obtained by using

the 3.5-cm³ volume cutpoint, as was the difference in local control rates. This study confirms previous findings that the involvement of certain specific sites is associated with a decrease in the local control rate.[13] Tumor involvement of the paraglottic space at the level of the false vocal cords ($p = 0.010$) was the most significant individual site. Involvement of the paraglottic space at this level indicates spread across the laryngeal ventricle. Prior reported experience indicated that these lesions may respond less well to RT compared to glottic tumors confined to the true cords and subglottic region.[29,30] Tumor involvement of the face of the arytenoid was also significant for decrease in local control ($p = 0.024$). Tumor presence in the interarytenoid region was also significant ($p = 0.020$). However, only six patients in the study population had this subsite involved. The combination of involvement of the paraglottic space from the false cord level to the subglottic region proved to be marginally significant ($p = 0.050$). These sites, although individually significant, did not provide significant additional information regarding the probability of local control when considered simultaneously with tumor volume.

Sclerosis of laryngeal cartilage

Twenty-six patients had sclerosis of one ($n = 14$) or two ($n = 12$) laryngeal cartilages. For patients with single-cartilage sclerosis, the local control rate was 72%. This did not differ significantly from the local control rate for patients with no cartilage sclerosis. This agrees with previous reports which suggest that CT-depicted isolated cartilage sclerosis in patients treated with RT alone does not adversely affect the rate of local control.[31] However, in patients with sclerosis of more than one laryngeal cartilage, the local control rate was significantly lower than in patients with no or single cartilage sclerosis. Recent studies have shown that approximately one third to one half of sclerotic laryngeal cartilages demonstrate microscopic invasion by tumor.[14,15] It is therefore reasonable to assume that if more than one cartilage is sclerotic, the chances of microscopic cartilage invasion will increase.

Four patients who were controlled at the primary site underwent total laryngectomy for suspected recurrence and/or laryngeal necrosis, and no tumor was found in the specimen. Two patients had relatively low-volume tumors, whereas the other two patients had high-volume tumors. This suggests that tumor volume alone has limitations for predicting an increased risk for chondronecrosis. Three of these patients with volumes of 3.0, 7.5 (Figure 3), and 7.9 cm³ also had sclerosis of the ipsilateral arytenoid and adjacent cricoid cartilage. The other patient with a 2.2-cm³ tumor had no cartilage sclerosis. Sclerosis of laryngeal cartilages, with its inherent increased risk for microscopic cartilage invasion, may predict an additional

risk for laryngeal chondronecrosis, since 3 of 4 of these patients had combined sclerosis of the ipsilateral arytenoid and cricoid.

Laryngeal cartilage sclerosis may then be logically regarded as a separate risk factor, in particular, worsening the chances of local control and increasing the risk for laryngeal chondronecrosis if more than one of the laryngeal cartilages is sclerotic. The presence of cartilage invasion, however, does not preclude the use of definitive RT, as was previously pointed out by Million[32], so that any indicator of early invasion remains only a risk factor and not a contraindication to definitive RT.

Concept of a CT-risk profile

The variables discussed above should be used together and considered with other biological and clinical factors to select good candidates for RT. In an attempt to identify informative risk groups based on imaging criteria, three groups were identified in our study population with what can be characterized as low, moderate and high risk for local failure (Table 4).

Inclusion in one of the three groups was based on two main risk factors: (a) volume: low volume (< 3.5 cm^3) vs. high volume (≥ 3.5 cm^3); and (b) cartilage sclerosis: no cartilage sclerosis/sclerosis of a single cartilage (arytenoid or cricoid) vs. > 1 cartilage sclerosis (ipsilateral arytenoid and adjacent cricoid cartilage). In the low-risk group we included patients with tumor volumes < 3.5 cm^3 and either no cartilage sclerosis or sclerosis of a single cartilage. The moderate-risk group consisted of patients with low-volume tumors and sclerosis of two laryngeal cartilages, patients with high-volume tumors and no sclerosis, and patients with a high-volume tumor with single cartilage sclerosis. Patients in the high-risk group had a combination of a high- volume tumor and combined sclerosis of the ipsilateral arytenoid and adjacent cricoid. The local control rates in these low-, moderate-, and high-risk groups were 90%, 43%, and 14%, respectively (Table 4). Although the linear trend in these local control rates from the low-risk group to the moderate- and high-risk group was statistically significant, the difference in local control for the moderate- and high risk-group itself was not. More data are required to determine if this CT-risk profile can be used to differentiate specifically between patients who are at moderate vs. high risk for local failure.

If the patients in these two latter groups, after being presented with their treatment options, elect to proceed with RT, they are considered at high risk ($\geq 50\%$) for failure at the primary site. At our institution, these patients are followed with a CT every 3 - 4 months following a baseline study done 3 months after completion of RT, in addition to their usual monthly return clinic visits. The incremental value of

such serial CT examinations in detecting recurrence, while it is still curable by salvage surgery, is currently under investigation.

The volume data reported here are currently used at our institution for two main purposes: (a) to ensure a more accurate informed consent process when the relative value of surgery and RT for likelihood of local control are being discussed with the patient; and (b) to identify the group of patients who are treated with definitive RT and are at high risk for local failure. This latter group may benefit from post-treatment imaging surveillance with CT, so that salvage can be instituted as soon as possible following local recurrence.

Volume data might also be used for triaging larger volume tumors to pre-RT chemotherapy to help select tumors in this high-risk group which are more likely to be amenable to laryngeal preservation by combined chemotherapy and RT. Results from the Veterans Administration Laryngeal Cancer Study Group[5] and Memorial Sloan-Kettering Hospital[6] are promising. A volume reduction of 50% or more by neoadjuvant chemotherapy, which can be quantitatively assessed by follow-up CT, is generally accepted as an indication to proceed with high-dose RT.[33] Nonresponders to chemotherapy would be offered radical surgery for cure.

The technique required to measure tumor volume is simple, provided that good-quality images are available. No attempt is made to differentiate between tumor and edema. Surgical and radiation oncologists, as well as diagnostic radiology trainees in our program, have mastered the skill in a short period of time. Knowledge of normal anatomy as well as some understanding of the natural history (spread pattern) of laryngeal cancer is required. If an appropriate workstation or digitizer is available, the measurement can be performed in 5-10 min. The cost is minimal and these techniques can be easily programmed into current CT scanner software as soon as there is sufficient demand. All modern stand alone workstations have this very simple capability.

In summary, the current study confirms that an acceptable local control rate can be expected in T3 squamous cell carcinoma of the glottic larynx when treated with RT alone. Local control rates can be improved by using a CT-based tumor profile; the ideal CT-profile for a radiocurable T3 glottic larynx carcinoma is: volume < 3.5 cm^3 and no or single laryngeal cartilage sclerosis. The local control rate achieved for such a CT favorable glottic lesion in this study was 90%.

There seem to be factors that cause primary site failure which cannot be explained on the basis of pathoanatomic extent, tumor volume, or a combination of the two. This is likely due to more biologically aggressive tumors or tumor-host interactions which are not fully understood. Perhaps, identification of biological markers will

help to define the small group of patients who are likely to fail despite having lesions which are favorable for cure on the basis of current clinical-diagnostic evaluation.

Ultimately, the anatomic information available from imaging needs to be combined with volumetric and biological data to allow for the most accurate pretreatment assessment of laryngeal cancer. In the future, this analysis will likely provide the most rational basis for clinical decision making when combined with patient preference and available treatment resources and experience.

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CHAPTER 4

Evaluation of pretreatment computed tomography as a predictor of local control in T1/T2 pyriform sinus carcinoma treated with definitive radiotherapy

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ABSTRACT

Background

To determine if pretreatment computed tomography (CT) findings can predict local control in pyriform sinus carcinoma treated with definitive radiotherapy (RT).

Materials and Methods

Twenty-three patients with pyriform sinus carcinoma (T1: $n = 5$, T2: $n = 18$) were treated with high-dose RT and followed for a minimum of 2 years. Tumor volumes and extent were determined on pretreatment CT studies. The specific CT parameters assessed were analyzed as predictors of local control.

Results

There was a significant decrease in local control rate for tumors ≥ 6.5 cm^3 (1 of 4 [25%]) relative to tumors < 6.5 cm^3 (17 of 19 [89%]; $p = 0.021$). Sensitivity and specificity for local control using this cutoff were 94% and 60%, respectively. Tumor score, as a measure of anatomic extent, was also found to be a significant predictor of local control ($p = 0.033$). The local control rate was not influenced significantly by the presence of "minimal" apex disease (< 10 mm in greatest dimensions as measured on CT) but decreased significantly when "bulk" apex disease (≥ 10 mm) was present ($p = 0.027$). Laryngeal cartilage sclerosis was not a significant predictor of outcome.

Conclusion

Pretreatment CT can stratify pyriform sinus carcinomas into groups more or less likely to be locally controlled with definitive RT.

INTRODUCTION

The majority of patients with pyriform sinus carcinoma are treated with either a total laryngectomy and partial pharyngectomy or partial laryngopharyngectomy depending on the extent of the lesion.[1] Radiation therapy (RT) is an effective, noninvasive treatment for early (T1, T2) pyriform sinus carcinoma with local control rates similar to those achieved with conservation surgery.[2] Radiotherapy, like conservation surgery, allows for the preservation of laryngeal function. Moreover, patients who refuse surgery or who are poor surgical candidates because of underlying medical conditions may be treated with RT.

Other centers have achieved local control rates with definitive RT for pyriform sinus carcinoma ranging from 68% to 73%.[3,4] The selection criteria for treatment with definitive RT have historically been based on clinical examination and the patient's willingness to return for frequent follow-up visits.[5] However, surgical salvage performed as a result of local failure following RT has a greater complication rate when compared to a similar procedure performed on the unirradiated patient.[5] Stratification of patients into high versus low risk for failure at the primary site with definitive RT might improve local control rates by triaging some patients to a perhaps more appropriate surgical procedure and might reduce the number of patients requiring salvage laryngectomy for ultimate local control.

Pretreatment computed tomography (CT) volumetric analysis of the primary tumor has been suggested as an effective predictor of local control in a variety of laryngeal tumors treated with RT alone.[5-8] Lee et al.[5] demonstrated significant differences in local control rates for T3 glottic tumors based on pretreatment CT tumor volume and analysis of the lesion spread pattern. Tumors with volumes less than 3.5 cm^3 had a higher likelihood of control compared to tumors with volumes ≥ 3.5 cm^3 (92% versus 33%, respectively). In a similar study, Freeman et al.[6] were able to identify those patients with supraglottic carcinomas who had a higher likelihood of local control based on pretreatment tumor volume. Tumors with volumes < 6 cm^3 had an 83% rate of local control, whereas those lesions with volumes ≥ 6 cm^3 had only a 46% control rate. In a follow-up study of 63 patients, this trend was confirmed; 89% of primary tumors < 6 cm^3 were controlled with laryngeal preservation by definitive RT, whereas only 40% of patients with tumor volumes ≥ 6 cm^3 were controlled and retained their larynges ($p < 0.0001$).[9]

The purpose of this study was to determine whether CT volumetric analysis and/or a tumor score (based on the involvement of specific anatomic sites within the larynx and hypopharynx) can be used to help predict local control in patients treated with definitive RT for pyriform sinus squamous cell carcinoma. The influence

of radiographic pyriform sinus apex involvement and sclerosis of adjacent laryngeal cartilages on radiocurability was also analyzed. These variables, if significant, could be combined to create a pretreatment CT-profile for early (T1, T2) pyriform sinus carcinoma that stratifies patients into groups very likely ("favorable") and those much less likely ("unfavorable") to be controlled at the primary site with definitive RT.

MATERIALS AND METHODS

Thirty-two patients with squamous cell carcinoma of the pyriform sinus who were treated with definitive RT from 1984 to 1993 underwent clinical staging and pretreatment, contrast-enhanced CT. Patients were followed for a minimum of 2 years after the completion of therapy, or untill local recurrence (median, 2 years and 10 months; range, 3 months - 8 years and 1 month). Tumor staging was based on guidelines of the American Joint Committee on Cancer.[10] Nine patients who died of intercurrent disease before the 2-year minimum were excluded from the analysis, even though all were continuously disease-free at the primary site. After these exclusions, 23 patients remained and are the subjects of this report. The overall number of patients per stage were as follows: T1, $n = 5$; T2, $n = 18$. The pretreatment radiographic and clinical profile of the tumors included in this study are summarized in Table 1.

Not discussed in the section above are a few patients who were clinically thought to have T1/T2 lesions and who, on CT, were found to have definite laryngeal cartilage invasion or gross extralaryngeal spread. These patients were up-staged to T4 based on imaging findings and received surgery followed by RT, or palliative RT. None of these were treated with definitive RT.

All patients underwent pretreatment contrast-enhanced CT of the larynx (3-5 mm thick contiguous sections; FOV, 16-20 cm; matrix size, 320 x 320 mm or 512 x 512 mm). All pretreatment studies were retrospectively reviewed by two of the authors (A.A.M., F.A.P.), who were blinded to patient outcome. Tumor volumes and anatomic spread pattern of the tumor as defined by involvement at specific sites were recorded by consensus reached between the two reviewers for each patient.

The anatomic sites evaluated included: (a) paraglottic space at the level of the true vocal cords, (b) paraglottic space at the level of the false vocal cords, (c) aryepiglottic fold, (d) pharyngoepiglottic fold, (e) posterior pharyngeal wall, (f) posterior laryngeal wall, (g) cricothyroid space, and (h) pyriform sinus apex. A total score was assigned to each tumor based on the number of anatomic sites involved (maximum score = 8). For example, a tumor involving the paraglottic space at both

TABLE 1

Preradiotherapy profile of pyriform sinus carcinomas

Patient no.	T Stage	Histologic differentiation (grade)*	CT apical involvement (mm)	Endoscopic apical involvement	Cartilage sclerosis (+/-)	Tumor score	Tumor volume (cm^3)	Local control
1	T1	Poor	No	No	–	1	0.50	Yes
2	T1	Mod	No	No	+	0	0.89	Yes
3	T1	Poor	No	No	–	2	0.95	Yes
4	T2	Poor	No	No	–	1	1.13	Yes
5	T2	Well	No	No	–	1	1.25	Yes
6	T1	Well	No	Yes	–	0	1.45	No
7	T2	Poor	No	No	–	1	1.92	Yes
8	T2	Poor	No	No	–	2	2.68	Yes
9	T2	Poor	Yes (4 x 4)	No	+	3	2.90	Yes
10	T1	Mod	Yes (3 x 3)	Not visualized †	–	4	3.02	Yes
11	T2	Poor	No	Not visualized	–	1	3.17	Yes
12	T2	Mod	No	Yes	–	1	3.66	Yes
13	T2	Poor	Yes (3 x 6)	Not visualized	+	3	4.44	Yes
14	T2	Poor	No	No	+	1	4.62	Yes
15	T2	Poor	Yes (8 x 10)	No	+	4	4.78	No
16	T2	Mod	Yes‡	Not visualized	+	2	4.93	Yes
17	T2	Mod	Yes (6 x 8)	No	+	5	5.85	Yes
18	T2	Mod	Yes (8 x 12)	Yes	–	7	5.99	Yes
19	T2	Mod	No	Not visualized	–	3	6.22	Yes
20	T2	Well	Yes (5 x 8)	No	–	5	6.94	No
21	T2	Mod	Yes (7 x 13)	Not visualized	+	5	7.50	No
22	T2	Mod	Yes (8 x 10)	Yes	+	4	8.85	No
23	T2	Poor	Yes (4 x 4)	No	+	6	9.38	Yes

** Differentiation grades: well, moderate, and poor.*

† At direct laryngoscopy, apex would not open adequately for complete inspection.

‡ CT not available to quantify apex involvement.

the false and true cord level and the aryepiglottic fold received a tumor score of 3. If a tumor was not visible on CT, i.e., superficial mucosal lesion, it was arbitrarily assigned a volume of 0.5 cm^3 and a score of zero. A tumor score of zero for a tumor with measurable volume was possible if the lesion was confined strictly to the anterior and lateral wall of the pyriform sinus.

Computed tomographic evidence of pyriform sinus apex disease was also recorded separately. Radiographic apex involvement was defined as the presence of a mass or obliteration of deep tissue planes at the level of the base of the arytenoid cartilage and upper 3 mm of the cricoid cartilage. If a mass was present at the apex, both the largest dimension and the second-largest dimension perpendicular to the first were recorded in millimeters. Involvement of the apex was divided into "minimal" (< 10 mm in largest dimension) and "bulk" (≥ 10 mm in largest dimension) disease categories. In one of 12 patients, this measurement could not be performed, because the original CT scan had been destroyed after the initial volume and score were recorded but before the apex measurement could be made (Table 1). Sclerosis of any laryngeal cartilage adjacent to tumor was recorded.

Volumetric analysis was performed on all primary tumors by outlining the lesion on each image where it was visible. There was no attempt to differentiate tumor from edema. The outlines were then transferred into a treatment-planning digitizer, and the final tumor volumes were generated in cubic centimeters (cm^3) after correcting for a magnification factor and slice thickness.

All patients were treated with RT alone. Treatment consisted of continuous course RT of once- (n = 7) or twice-a-day (n = 16) fractionation over a 5-week treatment period (total dose = 6,500 - 7,680 cGy). In some patients, this was followed by a planned neck dissection. The treatment techniques have been described in other publications.[1,2] The end point for all statistical analyses was defined as the achievement of or failure to achieve local control within 2 years after treatment.

Statistical Methods

Local control rates were compared between patient strata defined by the various pretreatment CT parameters using Fisher's exact test. Each observed tumor score and volume were also used as a cutoff to define low-risk and high-risk patient strata, which were then compared in a similar manner. Sensitivity and specificity for local control were computed for each cutoff, and optimal tumor score and volume cutoffs were then determined based on statistical significance and maximum difference in local control rates between cutoff-defined strata. An exact test for linear trend in ordered proportions available in the EGRET epidemiological statistics software package (Statistics and Epidemiology Research Corporation, Seattle WA, 1995) was used to test for the presence of a linear trend in local control rates among 3 ordered risk groups defined by tumor volume and bulk apex disease.

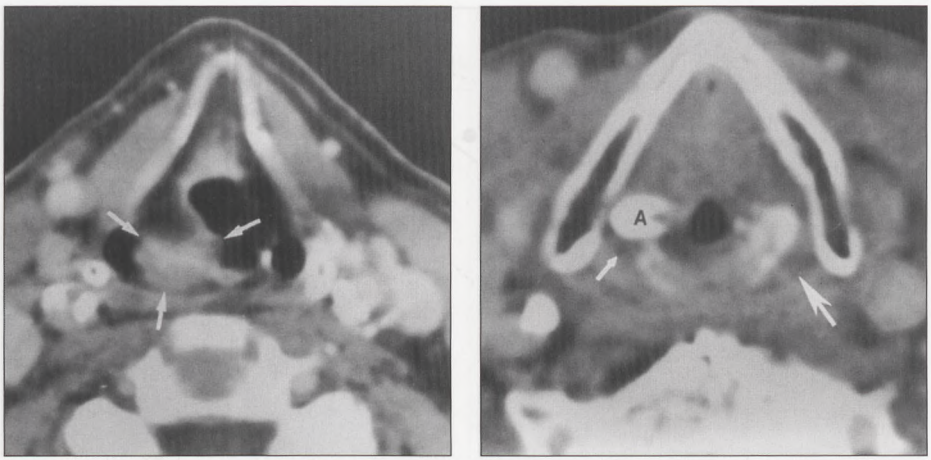


FIGURE 1. Sequential CT images of a 4.6-cm^3 pyriform sinus tumor which was succesfully controlled with definitive RT. (**A**) There is an exophytic lesion (arrows) involving the medial wall of the right mid-pyriform sinus. (**B**)At the level of the pyriform sinus apex (small arrow), no tumor is seen. The appearance is similar to the opposite apex (large arrow). There is associated sclerosis of the right arytenoid cartilage (A).

Logistic regression was used to determine whether total tumor volume was linearly associated with the log-odds of local control and to determine whether the relationship between tumor volume and the probability of local control differed significantly between pyriform sinus and supraglottic tumors over equivalent ranges of tumor volume (0-10 cm^3). The Spearman rank correlation coefficient was used to assess linear correlation between tumor volume and tumor score.

RESULTS

Eighteen of 23 patients (78%) treated with definitive RT were successfully controlled at the primary site (Figure 1). There were no patients who experienced a major treatment complication (e.g., laryngeal necrosis or severe laryngeal edema). The five patients who failed treatment at the primary site had volumes of 1.45 cm^3, 4.78 cm^3, 6.94 cm^3, 7.50 cm^3, and 8.85 cm^3 (Figure 2).

Total tumor volume was found to be a significant predictor of local control when stratified by optimal cutoff. The local control rate was 89% (17/19) for tumors with volumes < 6.5 cm^3 and 25% (1/4) for tumors ≥ 6.5 cm^3 (p = 0.021). The sensitivity and specificity for local control using this tumor-volume cutoff were 94% and 60%, respectively. Tumor volume over the entire range of observed

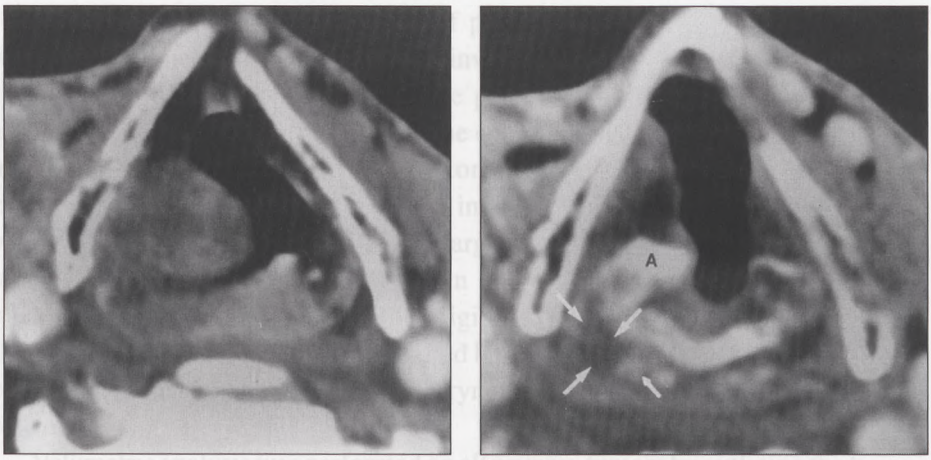
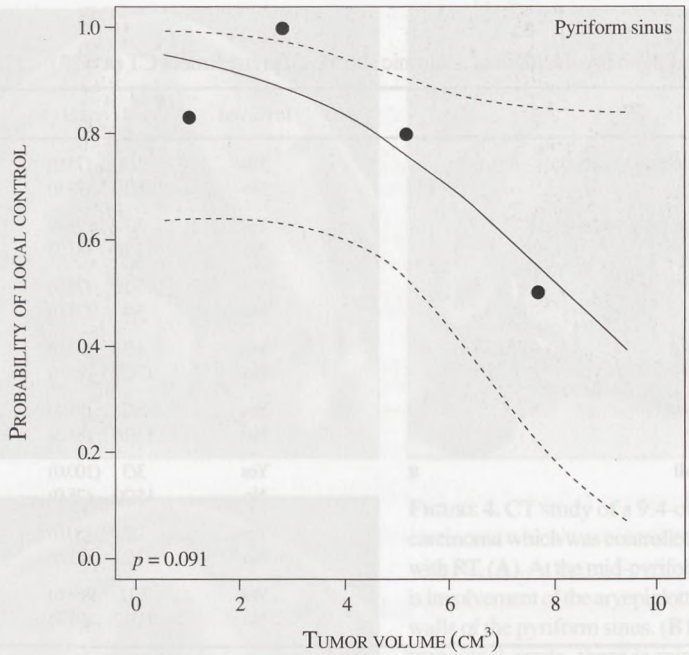


FIGURE 2. CT images of a 8.9-cm^3 pyriform sinus tumor which failed RT. (**A**) Section through the mid-pyriform sinus shows the tumor bulk involving the entire right pyriform sinus with extension onto the posterior pharyngeal wall as well as the aryepiglottic fold. (**B**) The true cord level shows bulk (8 x 10 mm) involvement of the pyriform sinus apex, with a discrete mass (small arrow) and obliteration of the deep tissue planes (large arrows). There is associated sclerosis of the ipsilateral arytenoid cartilage (A).

values was a marginally significant linear predictor of the log-odds of local control ($p = 0.091$). Figure 3A and 3B illustrate the predicted probability for local control as a function of tumor volume along with observed proportions for local control in 23 patients with pyriform sinus carcinoma and 53 patients with supraglottic carcinoma (data from a separate study).[9] Logistic regression results indicated no significant difference between pyriform sinus (Figure 3A) and supraglottic tumors (Figure 3B) regarding the relationship between tumor volume and probability of local control, both when volume was considered as a linear predictor of local control ($p = 0.939$) and when patients were stratified by the 6.5-cm^3 volume cutoff ($p = 0.671$).

FIGURE 3. Predicted probabilities for local control as a function of tumor volume for 23 patients with pyriform sinus carcinoma (**A**) and 53 patients with supraglottic carcinoma (**B**) (data extracted from Mancuso et al [9]). Solid lines show predicted probabilities for local control as a function of pretreatment CT; dashed lines show 95% confidence bands. Predicted probabilities were estimated by modeling the log-odds of local control as a linear function of tumor volume. Significance of the fitted models is indicated by the *p* value displayed in each plot. Individual points represent the proportion of patients who achieved local control in subgroups defined by ordered tumor-volume intervals. Each point represents 5 or 6 patients for pyriform sinus tumors and 8 or 9 patients for supraglottic tumors. Multiple logistic regression indicated no significant difference between the pyriform sinus and supraglottic predicted probability curves ($p = 0.939$).


Pyriform sinus
PROBABILITY OF LOCAL CONTROL
1.0
0.8
0.6
0.4
0.2
0.0
p = 0.091
0
2
4
6
8
10
TUMOR VOLUME (CM3)

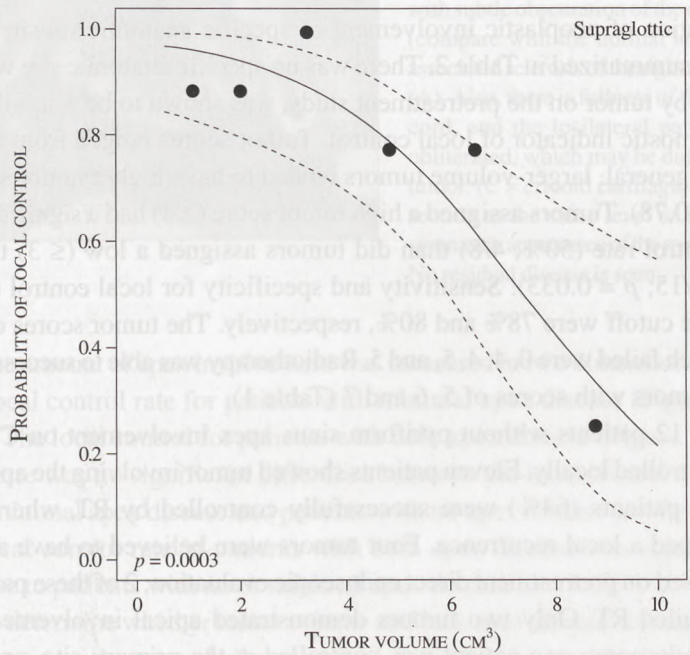

Supraglottic
PROBABILITY OF LOCAL CONTROL
1.0
0.8
0.6
0.4
0.2
0.0
p = 0.0003
0
2
4
6
8
10
TUMOR VOLUME (CM3)

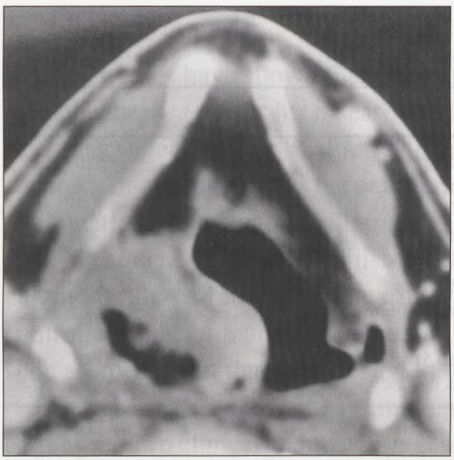
TABLE 2

Local control according to involvement of anatomic subsite on pretreatment CT ($n = 23$)

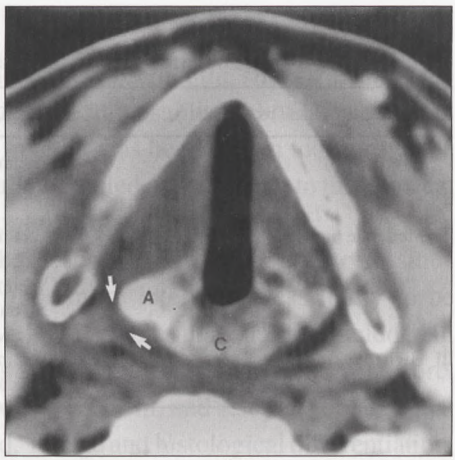
Site	Involved	Local control (%)	p Value
Paraglottic space at the true vocal cords	Yes	3/4 (75.0)	0.999
	No	15/19 (78.9)	
Paraglottic space at the false vocal cords	Yes	5/7 (71.4)	0.621
	No	13/16 (81.3)	
Aryepiglottic fold	Yes	15/19 (78.9)	0.999
	No	3/4 (75.0)	
Pharyngoepiglottic fold	Yes	1/3 (33.3)	0.107
	No	17/20 (85.0)	
Posterior pharyngeal wall	Yes	5/7 (71.4)	0.621
	No	13/16 (81.3)	
Posterior laryngeal wall	Yes	3/3 (100.0)	0.999
	No	15/20 (75.0)	
Cricothyroid space	Yes	1/2 (50.0)	0.395
	No	17/21 (81.0)	
Pyriform sinus apex	Yes	7/11 (63.6)	0.155
	No	11/12 (91.7)	

The association of neoplastic involvement of specific anatomic subsites and local control is summarized in Table 2. There was no specific anatomic site which, when involved by tumor on the pretreatment study, was shown to be a significant individual prognostic indicator of local control. Tumor scores ranged from 0 to 7 (mean, 2.7). In general, larger-volume tumors tended to have higher tumor scores (Spearman R = 0.78). Tumors assigned a high tumor score (≥ 4) had a significantly lower local control rate (50%, 4/8) than did tumors assigned a low (≤ 3) tumor score (93%, 14/15; $p = 0.033$). Sensitivity and specificity for local control using this tumor score cutoff were 78% and 80%, respectively. The tumor scores of the five lesions which failed were 0, 4, 4, 5, and 5. Radiotherapy was able to successfully control three tumors with scores of 5, 6 and 7 (Table 1).

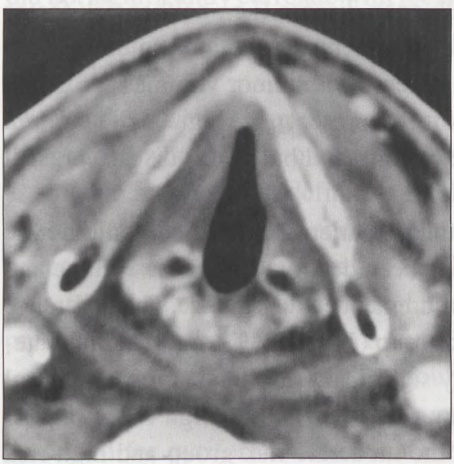
There were 12 patients without pyriform sinus apex involvement on CT; 11 (92%) were controlled locally. Eleven patients showed tumor involving the apex on CT; 7 of these patients (64%) were successfully controlled by RT, whereas 4 patients developed a local recurrence. Four tumors were believed to have apical involvement based on pretreatment direct endoscopic evaluation; 2 of these patients subsequently failed RT. Only two tumors demonstrated apical involvement on both CT and endoscopy; one patient was controlled at the primary site, and the other patient failed locally.



A



B



C

FIGURE 4. CT study of a 9.4-cm^3 pyriform sinus carcinoma which was controlled at the primary site with RT. (**A**). At the mid-pyriform sinus level there is involvement of the aryepiglottic fold and all three walls of the pyriform sinus. (**B**) At the level of the true vocal cords, there is minimal (4 x 4 mm) involvement of the pyriform sinus apex (arrows), with subtle obscuration of the deep tissue planes (compare with the normal left side). There is associated sclerosis of the right arytenoid cartilage (A). Also, there is fullness of the right true vocal cord, and the ipsilateral paraglottic space is obliterated, which may be due to edema and/or tumor. (C = cricoid cartilage). (**C**) Post-RT CT section at the same level as Figure 2B shows symmetric appearance of the pyriform sinus apices. No residual disease is seen.

The amount of apex involvement was measured in two dimensions in 10 patients. The local control rate for patients with minimal apex disease (Figure 4) was 83% (5/6). The local control for patients with bulk apex disease (Figure 2) was 25% (1/4). There was no significant difference between the local control rates of patients with minimal apex disease and patients with no apex disease ($p = 0.999$). However, the local control rate in patients with bulk apex disease was significantly lower relative to patients with no or minimal apex disease ($p = 0.027$).

To determine whether tumor volume and bulk apex disease simultaneously define informative risk groups for local control, local control rates for 3 patient strata ($n = 22$) were also compared (Table 3). The lowest risk stratum included 16 patients

TABLE 3

CT risk groups for patients with pyriform sinus carcinoma ($n = 22$)

Risk groups (for local recurrence)	Criteria	No. of patients	Local Control
I Low ($n = 16$)	Volume < 6.5 cm^3 No bulk apex disease	16	15/16 (94%)
II Moderate ($n = 4$)	Volume < 6.5 cm^3 Bulk apex disease	2	
	Volume ≥ 6.5 cm^3 No bulk apex disease	2	2/4 (50%)
III High ($n = 2$)	Volume ≥ 6.5 cm^3 Bulk apex disease	2	0/2 (0%)

with tumor volumes < 6.5 cm^3 and no bulk apex disease (i.e., neither risk factor present); the moderate risk stratum included 2 patients with tumor volumes < 6.5 cm^3 and bulk apex disease present plus 2 patients with tumor volumes ≥ 6.5 cm^3 and no bulk apex disease (i.e., only one risk factor present); the highest risk stratum included 2 patients with tumor volumes ≥ 6.5 cm^3 and bulk apex disease present (i.e., both risk factors present).

One patient had apex involvement (Table 1, patient no. 16) that could not be quantified, because the original CT scan had been destroyed after the volume and score were recorded but before the apex measurement could be made. The difference in local control rates between the low-risk group (15/16, 94%) and the moderate-risk group (2/4, 50%) was only marginally significant ($p = 0.088$). Local control rates did differ significantly between the low-risk group and the high-risk group (0/2, 0%; $p = 0.020$). Local control rates in the moderate-risk group and high-risk group did not differ significantly ($p = 0.467$). However, the linear trend in local control rates from the low-risk group to the moderate-risk group to the high-risk group was statistically significant ($p = 0.004$).

Ten tumors were associated with sclerosis of an adjacent laryngeal cartilage: ipsilateral arytenoid cartilage, $n = 8$ (Figure 2B); thyroid cartilage, $n = 1$; ipsilateral arytenoid and adjacent cricoid cartilage, $n = 1$. The 70% local control rate in these patients (7/10) did not differ significantly from the 85% local control rate in patients with no cartilage sclerosis (11/13; $p = 0.618$).

T Stage was not a significant predictor of local control ($p = 0.999$). 80% of T1 carcinomas (4/5) were controlled versus 78% of T2-staged lesions (14/18). Local control rates did not differ significantly by degree of histological differentiation ($p = 0.121$).

DISCUSSION

Several studies have shown that CT can accurately predict the site, size, and deep spread patterns (except for disease limited to the mucosal lining) of laryngeal and hypopharyngeal tumors.[11-17] Pretreatment imaging has been shown to improve the accuracy of staging and has become generally accepted as an adjunct to the physical examination for evaluation of laryngeal tumors at many institutions.[11-17]

This study sought to establish a CT-based profile for T1/T2 pyriform sinus carcinoma that stratifies patients into groups more likely and less likely to be controlled at the primary site with definitive RT. Variables that could be included in such a profile, and that were tested in this study, are tumor volume, tumor score, radiographic extent of pyriform sinus apex involvement, and sclerosis of laryngeal cartilages. Two clinical parameters assessed, T stage and histological differentiation, did not significantly correlate with local control.

Tumor volume

The local control rate for all tumors in the current study was 78%. This suggests that patients who have been treated at our institution have been satisfactorily assessed as suitable for cure with definitive RT. For tumors < 6.5 cm^3, the control rate was 89% (17/19). In contrast, one of four tumors ≥ 6.5 cm^3 were controlled at the primary site (local control rate, 25%). This difference in likelihood of local control was significant with a p value = 0.021, thus identifying tumor volume as an individual predictor of local control when using RT alone.

The local control rate of 89% found in this study for low-volume pyriform sinus tumors treated with RT is comparable to local control rates previously described for pyriform sinus tumors treated with conservation surgery.[18,19] This local control rate is an improvement over those previously reported series of pyriform sinus tumors treated only with RT by Bataini et al.[3] and Dubois et al.[4] (68% and 73%, respectively), where less favorable patients may have been included in the study populations.

Pretreatment tumor volumes are likely to assume a role similar to that suggested for supraglottic[6,9] and T3 glottic carcinomas[5] in helping to predict local control for pyriform sinus carcinomas. The critical volume, somewhere between 6 and 7 cm^3, for separating the favorable and unfavorable groups is similar to that found in supraglottic tumors.[6,9] The relationship between tumor volume and local control appearing to be inverse and roughly linear in the reported experience with supraglottic cancers is supported by the findings in this study. Plots of local control probability versus tumor volume over equivalent volume ranges show similar curves for both

pyriform sinus and supraglottic carcinomas (Figure 3). Multiple logistic regression indicated no significant difference between these curves ($p = 0.939$). On the other hand, the number of patients included in this study is small; therefore, the value of 6.5 cm^3 as a volume cutoff for T1/T2 pyriform sinus tumors should be used as a preliminary guideline. This trend might have important implications in the informed-consent process, because the patient can be presented with a more accurate assessment of the likelihood of local control with RT versus conservation or radical surgery.

A 1.45-cm^3 and a 4.78-cm^3 tumor failed locally (Table 1). The reason for these lower-volume tumors failing is unclear. The smallest of the two lesions may have been biologically aggressive, or perhaps there were other unfavorable tumor-host interactions which are currently incompletely understood. The 4.78-cm^3 tumor might also have been biologically aggressive, but CT showed bulk disease at the pyriform sinus apex, which seems to be an added risk factor for primary site failure, which will be discussed subsequently.

One of four tumors (25%) with volumes over 6.5 cm^3 were cured. The control of this 9.4-cm^3 tumor (Figure 4) agrees with the reported experience in supraglottic tumors that some high-volume lesions will be controlled at any laryngeal subsite.[9]

Tumor score

In general, higher tumor scores occurred in larger-volume tumors. Tumor score could effectively stratify patients into groups with a significant difference in local control rate: 93% versus 50%, respectively. However, the difference in local control rates was smaller than the one obtained by using the 6.5-cm^3 volume cutoff. When considered separately, there was no specific anatomic site which, when involved by tumor on the pretreatment study, was shown to be associated with a reduced chance of local control (Table 2).

Radiographic pyriform sinus apex involvement

The poor correlation seen in this study between apical involvement as determined by CT and by direct laryngoscopy is consistent with a prior study emphasizing this discrepancy.[17] The disparity is due to two main situations: tumor with minimal mucosal involvement of the apex, which is normally easily visualized by endoscopy but is not reliably detected by CT; and submucosal involvement of the apex detectable by CT (or Magnetic Resonance Imaging [MRI]), which is frequently clinically occult.

In this study, 11 of 23 patients (48%) had radiographic evidence of apex involvement. The 64% (7/11) local control rate in these patients did not differ significantly from the 92% local control rate for patients with no apex involvement ($p = 0.155$). However, when considered separately, patients with bulk apex disease had a significantly lower rate of local control than did patients with no or minimal apex disease. Thus, the presence or absence of bulk apex disease may be a significant individual predictor of local control when using RT alone. When tumor volume and bulk apex disease were used in combination to define three different risk groups, a significant, decreasing linear trend in the local control rate was observed as the number of these two risk factors increased from zero to one to two. Although the numbers are very small, this suggests that the combination of these two risk factors (i.e., high volume and bulk apex disease) creates an unfavorable risk profile for local control when treated with definitive RT.

Although there is general agreement in the surgical literature[20] that primary tumors with apex involvement should be treated with total laryngectomy and partial pharyngectomy, our findings suggest that this does not automatically apply to imaging (CT or MRI) evidence of apical involvement. Minimal apex disease, as defined previously, is likely to be controlled by RT (5 out of 6 patients in this study).

Sclerosis of laryngeal cartilage

In our series, 10 of 23 patients (43%) had sclerosis of one ($n = 9$) or two ($n = 1$) laryngeal cartilages. There was no significant difference in local control rate in these patients (70%) compared with the 85% local control rate for patients with no cartilage sclerosis. This agrees with previous reports assessing the significance of CT-depicted laryngeal cartilage sclerosis in patients treated with RT alone.[21] Recent studies have shown that approximately one third to one half of sclerotic laryngeal cartilages will demonstrate microscopic invasion by tumor.[15,16,22] Laryngeal cartilage sclerosis may therefore be regarded as a separate risk factor, perhaps marginally worsening the chances of local control in the profile of a pyriform sinus carcinoma, but the presence of cartilage sclerosis does not preclude the use of definitive RT. The combined results of this and other studies strongly support the opinion of Million[23] that microinvasion of the laryngeal cartilage is radiocurable.[15,16]

The technique required to measure tumor volumes is simple, provided that good quality images are available. A knowledge of normal anatomy as well as some understanding of the natural history (spread pattern) of pyriform sinus cancer are required. A number of authors have demonstrated that volume measurements of

head and neck tumors can be done routinely. [5-9, 22, 24] If an appropriate work station or digitizer is available, the measurement can be performed in 5-10 minutes. All modern, free-standing workstations have this very simple capability.

In conclusion, the current study confirms that a high local control rate can be expected in patients with T1/T2 pyriform sinus carcinoma when treated with RT alone. A possible, ideal CT profile for a radiocurable pyriform sinus carcinoma is: volume < 6.5 cm^3 and minimal (as previously defined) or no apex disease. The local control rate achieved for such a CT favorable pyriform lesion in this study was 94% (15/16).

Patients with less favorable lesions can be offered a trial of chemotherapy followed by triage to RT (in good responders) or surgery (in poor responders).[25]

There seem to be factors that cause primary-site failure which cannot be explained on the basis of pathoanatomic extent, tumor volume, or a combination of the two. Identification of biologic markers might help to define the small group of patients who are likely to fail despite having lesions which are favorable for cure on the basis of current clinical-diagnostic evaluation.

Ultimately the anatomic information available from imaging needs to be combined with volumetric and biologic data to allow for the most accurate pretreatment assessment of T1/T2 pyriform sinus cancer. In the future, this analysis will likely provide the most rational basis for clinical decision making when combined with patient preference and available treatment resources and experience.

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CHAPTER 5

Preradiotherapy computed tomography as a predictor of local control in supraglottic carcinoma

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ABSTRACT

Purpose

To determine the utility of pretreatment computed tomography (CT) for predicting primary site control in patients with supraglottic squamous cell carcinoma (SCC) treated with definitive radiotherapy (RT).

Materials and Methods

Pretreatment CT studies in 63 patients were reviewed. Minimum follow-up was two years. Local recurrence and treatment complications resulting in permanent loss of laryngeal function were documented. Tumor volume was calculated using a computer digitizer and pre-epiglottic space (PES) spread was estimated. The data were analyzed using a combination of Fisher's exact test, logistic regression modeling and multivariate analyses. Five-year local control rates were calculated using the product-limit method.

Results

Local control rates were inversely and roughly linearly related to tumor volume, although there seemed to be a threshold volume at which primary site prognosis diminished considerably. Local control was 89% in tumors < 6 cm^3 and 52% when volumes were ≥ 6 cm^3 ($p = 0.0012$). The likelihood of maintaining laryngeal function also varied with tumor volume: 89% for tumors < 6 cm^3 and 40% for tumors ≥ 6cm^3 ($p = 0.00004$). Pre-epiglottic space involvement by tumor of ≥ 25% was associated with a reduced chance of saving the larynx ($p = 0.0076$). Multivariate analyses revealed that only tumor volume independently altered these end points.

Conclusion

Pretreatment CT measurements of tumor volume permits stratification of patients with supraglottic SCC treated with RT alone (which allows preservation of laryngeal function) into groups in which local control is more likely and less likely. Pre-epiglottic space spread is not a contraindication to using RT as the primary treatment for supraglottic SCC.

INTRODUCTION

The treatment of supraglottic laryngeal carcinomas varies amongst institutions. Radiotherapy (RT) has proven to be an effective treatment of T1, T2 and early T3 supraglottic carcinomas, with local control rates similar to those achieved with conservation surgery.[1-10] Radiotherapy, like conservation laryngectomy, allows preservation of laryngeal function. Moreover, patients who refuse surgery or who are otherwise poor candidates for supraglottic laryngectomy because of underlying medical conditions or the anatomic extent of disease may be treated effectively with RT. Because of these advantages and the existence of centers capable of modern treatment planning and delivery, a growing number of patients are being treated with RT alone.

Selection for treatment with definitive RT has historically been based primarily on clinical examination and the patient's willingness to return for frequent follow-up visits.[5, 8,10] However, surgical salvage treatment undertaken as a result of local failure after RT has a greater complication rate than does a similar procedure performed as the initial step of treatment. Our group has found that up to one third of the patients undergoing salvage laryngectomy after RT failures may experience a significant complication.[8] It would be helpful to select those patients with lesions most likely to be locally controlled with RT so that the number of patients eventually undergoing salvage laryngectomy, with its potential added risks, could be reduced.

Pretreatment computed tomography (CT) with volumetric analysis of the primary tumor has been shown to be a potentially effective predictor of local control in a variety of laryngeal tumors treated with RT alone.[11-13] Our study updates the previous report from our institution in which patients with supraglottic carcinomas were identified who had a higher likelihood of local control based on pretreatment tumor volume.[12] In that study, probability of local control was 83% for tumors with volumes < 6 cm^3 and 46% for lesions with volumes ≥ 6 cm^3. Similar results were obtained by another group.[11]

The purpose of this study was to determine whether pretreatment volumetric CT analysis and the amount of pre-epiglottic space (PES) involvement by tumor can be used to predict the likelihood of local control and preservation of laryngeal function in patients with a supraglottic carcinoma treated with RT.

MATERIALS AND METHODS

Sixty-three patients with SCC of the supraglottic larynx who were treated with definitive RT from 1982 to 1991 underwent pretreatment, contrast-enhanced CT and were followed for a minimum of 2 years after the completion of therapy.

Tumor staging was based on guidelines of the American Joint Committee on Cancer.[14] Patients with definite laryngeal cartilage invasion or extralaryngeal spread on CT were excluded from this study; these patients were never treated with definitive RT but received palliative RT or surgery with or without postoperative RT. The two T4 carcinomas included in this analysis were considered T4 because of tenderness of the larynx and/or fullness in the neck suggestive of framework invasion or direct spread of tumor into the adjacent soft tissues of the neck. Computed tomography did not confirm this clinical impression of framework invasion. The overall number of patients per stage was as follows: T1, $n = 1$; T2, $n = 23$; T3, $n = 37$; T4, $n = 2$.

All tumors were treated with 6,500 to 7,440 cGy through once- or twice-daily continuous-course irradiation. In some patients, this was followed by a planned neck dissection. The treatment techniques have been described previously.[8]

Each patient underwent pretreatment, contrast-enhanced CT of the supraglottic larynx with 3- to 5-mm-thick contiguous sections. After 1986, all studies from this institution were performed with contiguous 3-mm sections, field of view of 16 to18 cm, and a 512 x 512-mm matrix. All pretreatment studies were retrospectively reviewed, and a consensus reached between two head and neck radiologists who were unaware of patient outcomes.

Volumes of all primary tumors were measured by outlining the lesion on each image where it was visible. No attempt was made to differentiate the tumor from related edema. Each study was evaluated and when necessary corrected for errors related to patient movement, respiratory misregistration, or technologist error in selection of slice location. The resulting stack of outlines was then transferred into a treatment-planning digitizer and the final tumor volumes (in cubic centimeters) were calculated after correcting for a magnification factor and the slice thickness.

Pre-epiglottic space (PES) spread was estimated and expressed as 0% to 25%, 25% to 75%, and > 75% involvement of the full volume of the PES.

Minimum length of follow-up for recurrent disease or major treatment complications was 2 years. Only those patients who were continuously disease-free for 2 years after the completion of RT were included. Patients who died from intercurrent disease before 2 years had passed were excluded from the analysis even though they were disease-free at the primary site. Major treatment complications included a laryngeal necrosis and/or edema that resulted in the complete, permanent loss of laryngeal function; ultimately, these patients were permanently tracheostomy-dependent or underwent laryngectomy. Mild laryngeal pain or hoarseness in a patient with an otherwise normally functioning larynx was classified as a minor complication and not considered in the outcome analysis.

TABLE 1

Local control as a function of T stage for low-volume and high-volume lesions ($n = 63$)

	Local control by tumor volume	
Stage	$< 6\ cm^3$	$\geq 6\ cm^3$
T1	1 / 1	0 / 0
T2	19 / 21	1 / 2
T3	13 / 15	12 / 22
T4	1 / 1	0 / 1
Total	34 / 38 (89%)	13 / 25 (52%)

One patient with a massive (65 cm^3) tumor was excluded from the analysis to avoid skewing of the volume data. This patient's disease was controlled at the primary site, and the patient remained disease-free but was permanently tracheostomy-dependent.

Statistical methods

Statistical analysis for local control rates and preservation of laryngeal function was performed using a combination of Fisher's exact test and logistic regression modeling. The rates of local control (63 patients) and local control with preservation of laryngeal function (60 patients) were also calculated, using the product-limit method.[15,16] Significance levels between the curves were calculated using the log-rank test.[16,17]

Multivariate analyses were performed using the forward stepwise log-rank test of the association of covariates.[18] The parameters evaluated in multivariate analyses were as follows: primary tumor volume ($< 6\ cm^3$ versus $\geq 6\ cm^3$), stage of regional lymph node involvement (N0 versus N+), vocal cord mobility (normal versus absent or impaired), primary T stage, PES invasion ($< 25\%$ versus $\geq 25\%$) and sex.

RESULTS

Overall, disease in 47 (75%) of the 63 patients was controlled with RT alone, whereas disease recurred in 16 patients (25%) at the primary site. The overall results of treatment and tumor volume with respect to T stage are listed in Table 1. Three patients whose disease was controlled at the primary site underwent total laryngectomy for laryngeal necrosis, and no tumor was found in the specimen

TABLE 2

Local tumor control and laryngeal function preservation versus tumor volume ($n = 63$)

	Tumor volume		
	$< 6\ cm^3$ ($n = 38$)	$\geq 6\ cm^3$ ($n = 25$)	
	No. of patients	No. of patients	p-value
Local control	34 (89%)	13 (52%)	0.0012
Functioning larynx	34 (89%)	10 (40%)	0.00004

obtained (Table 2). Thus, disease in 44 (70%) of 63 patients who were treated with definitive RT was controlled at the primary site with preservation of laryngeal function, whereas 19 patients (30%) lost laryngeal function because of either local failure ($n = 16$) or a treatment-related complication ($n = 3$).

The distribution of tumor volumes with respect to local control and preservation of laryngeal function is shown in Figure 1 and Table 2. The linear trend relating tumor volume to both the rate of local control and preservation of laryngeal function is shown in Figure 2. Increasing median tumor volumes were associated with a progressively lower likelihood of control at the primary site. For larger-volume tumors, an increase in median tumor volume was associated with an even lower likelihood of preservation of laryngeal function.

Disease in three patients with tumor volumes $\geq 6\ cm^3$ was locally controlled, but these patients required laryngectomy for laryngeal necrosis. Therefore, disease in 10 (40%) of the 25 patients with tumor volumes $\geq 6\ cm^3$ was ultimately controlled at the primary site with preservation of laryngeal function, whereas 15 (60%) of these 25 patients ultimately lost laryngeal function because of recurrent tumors or major treatment complications (Table 2). Because no patient with a tumor volume $< 6\ cm^3$ had a complication that resulted in permanent loss of laryngeal function, the probability of preserving laryngeal function for tumors with volumes $< 6\ cm^3$ remained at 89%, the same as that for primary site control. This difference in likelihood of preservation of laryngeal function based on a threshold volume of 6 cm^3 (89% versus 40%) was strongly significant ($p = 0.00004$).

Local control rates at 5 years were as follows: overall, 69%; T2 tumors $< 6\ cm^3$, 76%; T3 tumors $< 6\ cm^3$, 86%; and T3 tumors $\geq 6\ cm^3$, 48%. T3 tumors $< 6\ cm^3$ were significantly more likely to be locally controlled compared with those $\geq 6\ cm^3$ ($p = 0.0231$). Rates of local control with preservation of laryngeal function at 5 years were as follows: overall, 68%; T2 tumors $< 6\ cm^3$, 76%; T3 tumors $< 6\ cm^3$,

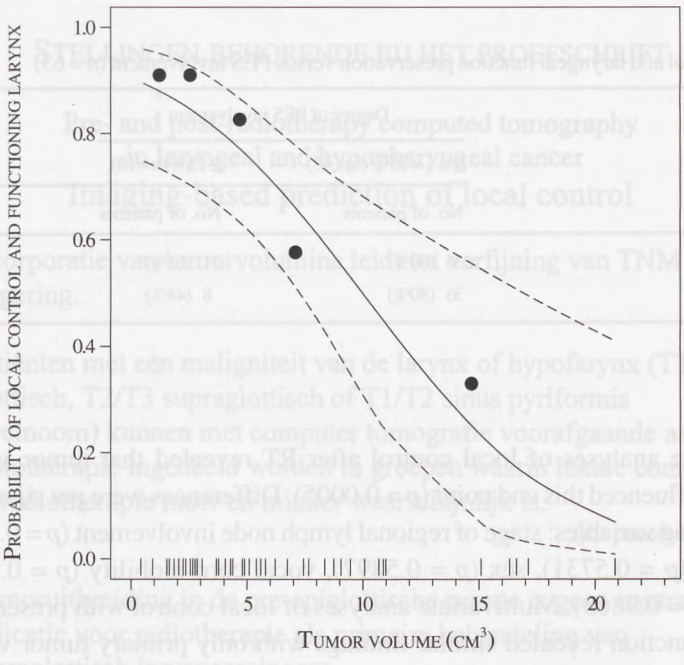

FIGURE 1. Predicted probability of achieving local control with a functioning larynx, plotted as a function of tumor volume. Predicted probabilities (solid line) and 95% confidence bands (dashed lines) were estimated via logistic regression. Individual points indicate median tumor volume and observed proportion of patients achieving local control with a functioning larynx within mutually exclusive groups of patient sorted by tumor volume (n = 12 to 13 per group). Vertical marks along the x-axis indicate observed volumes in the study population.

86%; and T3 tumors ≥ 6 cm³, 45%. The likelihood of local control with preservation of laryngeal function was significantly higher for T3 cancers < 6 cm³ compared with tumors ≥ 6 cm³ ($p^* = 0.0168$).

The effect of PES involvement by tumor on local control rates was also evaluated. Statistical analysis demonstrated no significant difference between the amount of PES involvement by the primary tumor and local control rates (p = 0.11) (Table 3). However, the degree of PES involvement seemed to affect the likelihood of preserving laryngeal function. No patient with < 25% PES involvement experienced a significant treatment complication; therefore, the overall chance of local control with preservation of laryngeal function remained at 80%. Three patients with > 25% PES involvement, whose disease was locally controlled, subsequently developed laryngeal necrosis and underwent total laryngectomy. This difference in organ preservation based on PES < 25% versus ≥ 25% was statistically significant (p = 0.0076) (Table 3).

TABLE 3

Local tumor control and laryngeal function preservation versus PES involvement ($n = 63$)

	Degree of PES involvement		
	0% - < 25% ($n = 45$)	≥ 25% ($n = 18$)	
	No. of patients	No. of patients	p-value
Local control	36 (80%)	11 (61%)	0.11
Functioning larynx	36 (80%)	8 (44%)	0.0076

Multivariate analyses of local control after RT revealed that tumor volume significantly influenced this end point ($p = 0.0005$). Differences were not significant for the remaining variables: stage of regional lymph node involvement ($p = 0.1706$), PES invasion ($p = 0.5731$), sex ($p = 0.5897$), vocal cord mobility ($p = 0.9046$), and T stage ($p = 0.9863$). Multivariate analyses of local control with preservation of laryngeal function revealed similar findings with only primary tumor volume being significant ($p = 0.0001$). Differences were not significant for stage of regional lymph node involvement ($p = 0.2073$), sex ($p = 0.4420$), vocal cord mobility ($p = 0.6888$), T stage ($p = 0.8888$), and PES invasion ($p = 0.9222$).

DISCUSSION

This study updated the earlier, smaller study at our institution concerning the value of CT in selecting patients for definitive RT of a supraglottic carcinoma.[12] In that study, measurement of tumor volume by CT, was found to permit stratification of patients with a supraglottic SCC into groups very likely (83%) and less likely (46%) to have disease controlled at the primary site with definitive RT; the threshold volume was 6 cm^3. Another group showed that tumor volume in a laryngeal carcinoma is important in predicting disease-free interval in T2 to T4 laryngeal (all sites) carcinomas treated with radical RT.[11] In that study, mean tumor volume for lesions controlled by RT was 8.9 cm^3. The suggested correlation between local control with RT alone and tumor volume as seen on CT was corroborated, but not quantitated, by our group in a previous report.[19] In 1971, Fletcher reported that volume of disease, rather than an arbitrary stage, was the overriding factor determining the radiocurability of uterine cervix SCC.[20] Tumor volume has a similar effect on the curability of a supraglottic SCC. The radiobiologic reasons for this are discussed elsewhere.[10,21]

STELLINGEN BEHORENDE BIJ HET PROEFSCHRIFT

Pre- and post-radiotherapy computed tomography
in laryngeal and hypopharyngeal cancer
Imaging-based prediction of local control

1. Incorporatie van tumorvolumina leidt tot verfijning van TNM stagering.

2. Patiënten met een maligniteit van de larynx of hypofarynx (T3 glottisch, T2/T3 supraglottisch of T1/T2 sinus pyriformis carcinoom) kunnen met computer tomografie voorafgaande aan radiotherapie ingedeeld worden in groepen waarin lokale controle na radiotherapie meer en minder waarschijnlijk is.
(dit proefschrift)

3. Tumoruitbreiding in de pre-epiglottische ruimte is geen contra-indicatie voor radiotherapie als primaire behandeling van supraglottisch larynxcarcinoom.
(dit proefschrift)

4. Met computer tomografie voor en na radiotherapie kunnen patiënten met larynxcarcinoom geïdentificeerd worden die een hoog risico hebben op het ontwikkelen van een lokaal recidief.
(dit proefschrift)

5. "Alle pathologische nieuwvormingen moeten zoo spoedig en zoo volledig mogelijk weggenomen worden".
Dr. Jan K. Pameijer, 'Over een geval van Sarcoma Cranii'.
Academisch proefschrift aan de Hoogeschool te Utrecht,
13 Mei 1869.

6. Behoud van functie en cosmetiek dient bij de behandeling van hoofd-halstumoren een belangrijke overweging te zijn.
Frank A. Pameijer, Proefschrift aan de Universiteit Utrecht,
9 november 1999.

7. Het opmeten van lengte en breedte van tumoren op CT/MRI scans doe je met een schuifmaat niet uit de losse pols.

8. De wetenschap is als een pad naar de horizon met links en rechts losliggende tegels. Met een proefschrift leg je één tegel vast.

9. Het schrijven van een proefschrift lijkt op een Hongaarse zigeunerserie. Het begint langzaam, zonder maat (Rubato). Het middendeel, een halfsnelle dans in 4/4 maat, heeft meer structuur (Palotas). Het eindigt met een snelle opzwepende dans (Estam), afgesloten met drie accoorden (Ho-ra Est / Spritsch Spratsch Sproetsch).

10. Het dieet van Montignac heeft hetzelfde werkingsmechanisme als een multidisciplinaire werkgroep. De combinatie van verschillende ingrediënten geeft een optimaal effect. Het effect van de werkgroep is blijvend.

Utrecht, 9 november 1999 Frank Pameijer

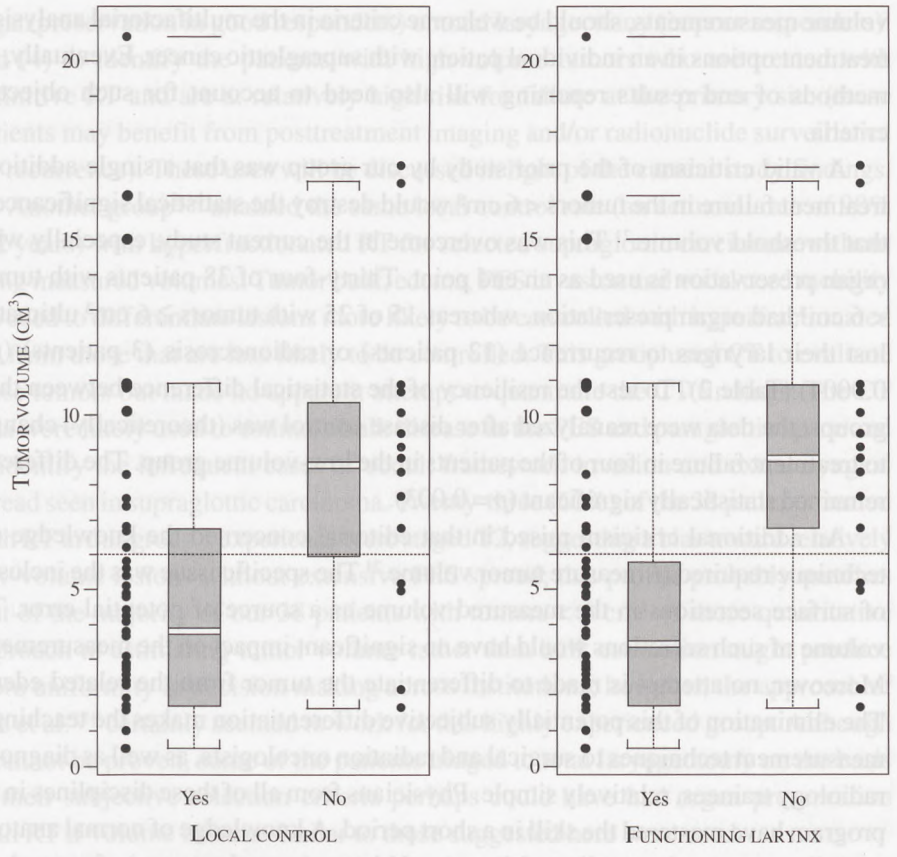

FIGURE 2. Boxplot distribution of tumor volumes by local control status and by functional larynx status. The horizontal white bar inside each box indicates the 50th percentile (median) of the distribution. The upper and lower ends of each box indicate the 25th and 75th percentiles and span the middle 50% of the distribution. Whiskers extending from either end of the box are drawn to the furthest data points still within +/- 2 box lengths from the middle of the box. Points beyond those limits are marked individually by horizontal lines.

Of the 63 patients in our study there were two with tumor volumes of approximately 2 cm^3 and two others with volumes of approximately 5 cm^3 in whom RT failed at the primary site. The smaller of these tumors were probably biologically aggressive and/or inherently insensitive to RT, factors that may be explained by cellular kinetics. These lesions might also have been affected by host/tumor/environmental factors such as suboptimal immune status. Many groups are working on ways to incorporate tumor and host biologic markers into the clinical-diagnostic decision-making process. These objective criteria, along with objective

volume measurements, should be welcome criteria in the multifactorial analysis of treatment options in an individual patient with supraglottic cancer. Eventually, the methods of end results reporting will also need to account for such objective criteria.

A valid criticism of the prior study by our group was that a single additional treatment failure in the tumors < 6 cm^3 would destroy the statistical significance of that threshold volume.[21] This was overcome in the current study, especially when organ preservation is used as an end point. Thirty-four of 38 patients with tumors < 6 cm^3 had organ preservation, whereas 15 of 25 with tumors ≥ 6 cm^3 ultimately lost their larynges to recurrence (12 patients) or radionecrosis (3 patients) (p = 0.0004) (Table 2). To test the resiliency of the statistical difference between these groups, the data were reanalyzed after disease control was (theoretically) changed to treatment failure in four of the patients in the low-volume group. The difference remained statistically significant ($p = 0.003$).

An additional criticism raised in that editorial concerned the knowledge and technique required to measure tumor volume.[21] The specific issue was the inclusion of surface secretions in the measured volume as a source of potential error. The volume of such secretions would have no significant impact on the measurements. Moreover, no attempt is made to differentiate the tumor from the related edema. The elimination of this potentially subjective differentiation makes the teaching of measurement techniques to surgical and radiation oncologists, as well as diagnostic radiology trainees, relatively simple. Physicians from all of these disciplines in our program have mastered the skill in a short period. A knowledge of normal anatomy as well as some understanding of the natural history (spread patterns) of supraglottic cancer is required. This knowledge is a requisite for any person who is involved in the care of patients with a supraglottic cancer. Tumor volume measurements may not be suitable for physicians who see only an occasional case of laryngeal carcinoma. However, these volumes can be measured by any expert, such as a radiologist, radiation oncologist or surgical oncologist, who regularly participates in the care of patients with head and neck cancer. Needed are good-quality images and an appropriate work station or digitizer.

The volume data reported here are currently used at our institution for several purposes: (1) to ensure a more accurate, informed consent process when the relative value of surgery and RT for local control and organ preservation is being discussed with the patient; (2) to help decide whether a patient who is medically, psychologically, and socially suitable for partial laryngectomy is more likely to be cured by that procedure than by RT or total laryngectomy; (3) to select patients with high-volume tumors for a trial of chemotherapy followed by triage to RT (for

organ preservation in good responders) or total laryngectomy (in poor responders); and (4) to identify the patients with high-volume tumors who are treated with definitive RT and are at relatively high risk for failure at the primary site (these patients may benefit from posttreatment imaging and/or radionuclide surveillance for recurrence). These uses will be discussed in light of the current study findings.

Another group[9,10] attained the same local control rate (an actuarial rate of 90% at 2 years) with hyperfractionated RT for selected supraglottic carcinoma without using measured volumes. Tumor bulk, edema, PES invasion and vocal cord mobility are used to differentiate lesions more likely to be controlled with hyperfractionated RT from those that are less likely to be controlled. This group used CT to evaluate these tumors but made no apparent attempt to quantitate the CT findings. The CT data were likely used to estimate bulk disease in the PES and paraglottic space and to identify the infrequent cases of occult framework invasion and extralaryngeal spread seen in supraglottic carcinoma. Twenty-three (61%) of the 38 patients treated with RT in this group's experience were staged T2, suggesting a bias toward relatively low-volume lesions without extensive PES spread; this profile probably matches that of the majority of our 38 patients with tumors < 6 cm^3. A more quantitative approach to estimating tumor volume rather than bulk estimation might produce more uniformity in decision making across institutions; however, the approach of Lee et al.[9,10] certainly seemed to work for this highly experienced group. Although it cannot be proven, some of the patients triaged to total laryngectomy on the basis of their subjective selection criteria perhaps could have had organ preservation with RT if volume criteria similar to those suggested here were used.

As a result of the collection of the data presented in the current report, patients at our institution who have higher-volume tumors and are suitable for partial laryngectomy are now informed of the potentially increased likelihood of organ preservation with that surgical procedure. This theoretical improvement in surgical organ preservation by such triage is yet to be proven. It is likely that many patients with higher-volume tumors will still require total laryngectomy for local control because they are anatomically or medically unsuitable for partial laryngectomy. A survival benefit may be difficult to prove because there are so few ultimate failures at the primary site in a well-screened group of patients with supraglottic cancer treated with hyperfractionated RT or partial laryngectomy. Survival is linked more to control of regional metastases (neck disease) than to primary site control in a supraglottic carcinoma.

Patients with higher-volume tumors are also being triaged to chemotherapy as a predictor of organ preservation with RT. Currently, such triage is not based on a specific threshold volume. The trend in our institution is to suggest this approach

for the larger tumors (> 12 to 14 cm^3) that would also necessitate total laryngectomy for local control. Follow-up CT in this group has the advantage of allowing a quantitative assessment of response to chemotherapy. Volume reduction of ≥ 50% is generally accepted as an indication to proceed with combined chemotherapy and hyperfractionated RT as a plan for organ preservation. A complete response to induction chemotherapy in hypopharyngeal cancer has recently been proven useful for selecting patients in whom the larynx may be preserved by a chemotherapy/RT regimen without a reduction in survival.[22]

Finally, patients with tumor volumes ≥ 6 cm^3 are considered to be at high risk (> 50%) for failure when they choose RT as the principal mode of therapy. This choice always follows a presentation of treatment options and their relative likelihoods of a cure with organ preservation. This high risk group is followed with CT, with a baseline study performed 3 to 4 months after the completion of RT and follow-up CT every 4 months after that for 2 years. A recent retrospective study suggests that if the baseline study shows complete resolution of the primary tumor, additional study is not necessary unless there is clinical suspicion of recurrence.[23,24] Approximately 30% of patients with a residual focal mass on the baseline study will develop a recurrence.[24] That same report also suggests criteria for separating routine postradiation changes from significant focal masses. Further study is required to determine whether serial CT can help diagnose local recurrence while it is curable by salvage laryngectomy. Preliminary data suggest that positron emission tomography or single photon emission CT-fluorodeoxyglucose radionuclide studies may be useful in surveillance for a recurrent tumor in this high-risk group.[25,26]

Features, other than the heretofore largely subjective estimation of bulk (large or deeply infiltrating tumors), associated with local failure following radical irradiation of a supraglottic carcinoma include T stage and invasion of the PES and tongue base.[1-4,7] On the basis of T stage alone, the historical cure rates for supraglottic carcinomas at our institution have been as follows: T1,100%; T2, 85% to 90%; and T3, 70%. When rates of local control, as traditionally reported on the basis of T stage, are compared with the results of this investigation, it becomes clear that the T3 carcinoma group is the most heterogeneous with respect to likelihood of local control with definitive RT (Table 1). This lack of predictability in the T3 group is related to the limitations of even the best laryngoscopic examination for evaluating the deep extent of disease, compared with modern sectional imaging techniques such as CT and magnetic resonance imaging (MRI).

The negative prognostic implications of extensive PES spread for both surgical and RT attempts at organ preservation have been emphasized in the literature. Few surgical or radiation oncologists have discussed their specific methods for evaluating

PES invasion, and none has presented a quantitative or semiquantitative pretherapy analysis based on CT findings. Computed tomography or MRI is the only means of precisely evaluating this space before pathologic staging; this has been known for approximately 20 years.[27]

In our study, PES involvement was estimated in 25% increments. For the final analysis, the group was split into those patients with limited (< 25%) and those with more extensive (≥ 25%) involvement. Using this classification, there was no statistically significant difference in local control rates based on involvement of the PES as an independent variable ($p = 0.11$ and $p = 0.5731$, depending on the method of data analysis) (Table 3). However, when organ preservation became the end point, PES involvement did reach statistical significance by one method of data analysis ($p = 0.0076$; Table 3). This was not the case in the multivariate analysis. Two of the three patients who lost their larynges due to radionecrosis had > 25% involvement (tumor volumes, 15.0 and 7.4 cm^3), and another had > 50% PES involvement (tumor volume, 10.8 cm^3). One of these three patients also had equivocal, but not definitive, CT evidence of laryngeal framework involvement, and in the other two patients tumors were immediately adjacent to the thyroid cartilage and thyrohyoid membrane.

High-volume PES invasion may serve to identify a subset of patients at high risk for framework invasion. In our practice, invasion of the PES increases staging from T2 to T3; disease in patients with obvious cartilage destruction or spread to the extralaryngeal soft tissues via the thyrohyoid membrane as seen on CT is staged T4. At least one group suggests that disease in all patients with PES spread should be staged T4, partially because of the risk of framework invasion.[28] This probably leads to overstaging if CT evidence of limited PES spread is used as a criterion. However, given that the larynx was preserved in only four (36%) of 11 patients with > 75% PES invasion,[28] this upstaging may be justified only in patients with such advanced PES involvement.

In summary, it is relatively simple, when good-quality CT images are available, to determine tumor volume in supraglottic carcinomas. In selected groups of patients with supraglottic carcinoma, mainly those tumors characterized as large T2 or T3 by traditional staging methods, tumor volume may be a prime consideration in the choice of the method for preserving the larynx and tumor volume does not have a significant effect on the risk of ultimate treatment failure. CT (or MRI) evaluation of the PES may also contribute to better treatment decisions in the same group of patients. Some effort should be made to integrate volume determinations into the system of end results reporting if the findings of this and previous similar studies are corroborated by other investigators.

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CHAPTER 6

Pre- and post-radiotherapy computed tomography in laryngeal cancer: Imaging-based prediction of local failure

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ABSTRACT

Purpose

To determine if pre-radiotherapy (RT) and/or post-radiotherapy computed tomography (CT) can predict local failure in patients with laryngeal carcinoma treated with definitive RT.

Materials and Methods

The pre- and post-RT CT examinations of 59 patients (T3 glottic carcinoma [n = 30] and T1 - T4 supraglottic carcinoma [n = 29]) were reviewed. For each patient, the first post-RT CT study between 1 and 6 months after irradiation was used. All patients were treated with definitive hyperfractionated twice-daily continuous-course irradiation to a total dose of 6,720 to 7,920 cGy, and followed-up clinically for at least 2 years after completion of RT. Local control was defined as absence of primary tumor recurrence and a functioning larynx. On the pretreatment CT study, each tumor was assigned a high- or low-risk profile for local failure after RT. The post-RT CT examinations were evaluated for posttreatment changes using a three-point post-RT CT-score: 1 = expected post-RT changes; 2 = focal mass with a maximal diameter of < 1 cm and/or asymmetric obliteration of laryngeal tissue planes; 3 = focal mass with a maximal diameter of > 1 cm, or < 50% estimated tumor volume reduction.

Results

The local control rates at 2 years post-RT based on pretreatment CT evaluation were 88% for low pretreatment risk profile patients (95% CI: 66 - 96%) and 34% (95% CI: 19 - 50%) for high pretreatment risk profile patients (risk ratio 6.583; 95% CI: 2.265 - 9.129; p = 0.0001). Based on posttreatment CT, the local control rates at 2 years post-RT were 94% for score 1, 67% for score 2 and 10% for score 3 (risk ratio 4.760; 95% CI: 2.278 - 9.950; p = 0.0001). Post-RT CT-scores added significant information to the pretreatment risk profiles on prognosis.

Conclusion

Pretreatment CT risk profiles, as well as post-RT CT evaluation can identify patients, irradiated for laryngeal carcinomas, at high risk for developing local failure. When the post-RT CT-score is available, it proves to be an even better prognosticator than the pretreatment CT risk profile.

INTRODUCTION

The treatment options for squamous cell carcinoma of the larynx include radiation therapy (RT), surgery, or a combination of both.[1] Radiotherapy, sometimes combined with chemotherapy in larynx preservation trials[2-4], provides a treatment alternative which allows for preservation of laryngeal function.

After RT, clinical examination of the larynx is difficult because of radiation effects which alter the mucosa and produce varying degrees of edema and fibrosis. Residual or recurrent tumor, therefore, can be difficult to detect by physical examination. Accurate interpretation of computed tomography (CT) studies in patients irradiated for laryngeal cancer requires that the expected radiographic changes due to treatment not be misinterpreted as residual or recurrent tumor. The expected post-RT appearance of the irradiated larynx on CT examinations, as well as the response of the primary site to irradiation have been described.[5,6] These data suggested that CT may be useful in the early differentiation of treatment responders from nonresponders. Other studies suggest that imaging-based identification of patients at high risk for local failure is possible before treatment with definitive RT.[7-12] In patients triaged to such a high-risk profile, intensive imaging surveillance could be added to the already careful clinical follow-up regimen, and possibly lead to earlier detection of local recurrence in nonresponders. In good responders and those patients with low-risk profiles, cost reductions could be achieved by limiting or eliminating the imaging surveillance, and the frequency of clinical follow-up may be diminished.

The purpose of this study was to determine if pre-RT and/or post-RT CT can predict local failure in patients with laryngeal carcinomas treated with definitive RT.

MATERIALS AND METHODS

The pretreatment and post-RT follow-up CT examinations of 59 patients were retrospectively analyzed. Thirty patients had glottic carcinoma (T3, $n = 30$) and 29 had supraglottic carcinoma (T1, $n = 1$; T2, $n = 9$; T3, $n = 16$; T4, $n = 3$). All lesions were initially resectable. The clinical staging was based on guidelines of the American Joint Committee on Cancer.[13] Before treatment every patient underwent a CT study of the head and neck. All patients were treated, between 1980 - 1993, at the University of Florida, with definitive hyperfractionated twice-daily continuous-course RT to a total dose of 6,720 to 7,920 cGy. The treatment techniques have been described previously.[14-16] In some patients, RT was followed by a planned neck dissection. One patient with a T3 supraglottic carcinoma received neoadjuvant chemotherapy prior to RT. The patients entered in the study had at

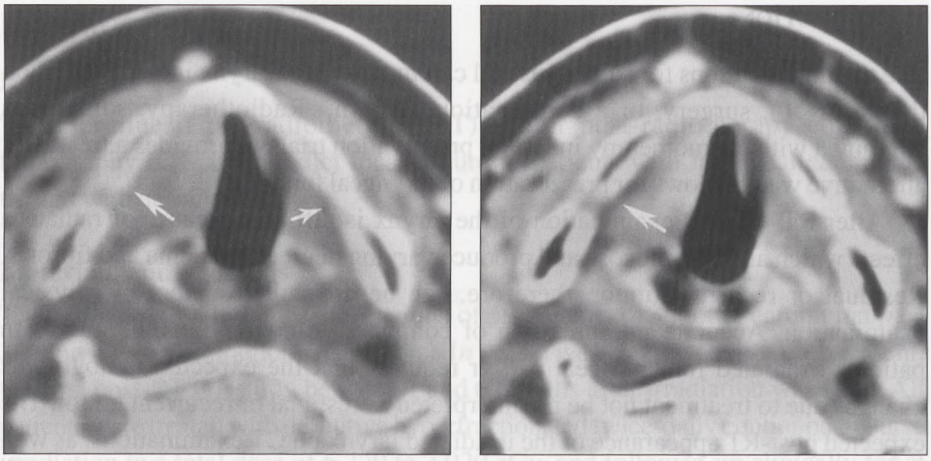

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FIGURE 1. CT images of a patient with a T3 carcinoma of the right true vocal cord and a low pretreatment risk profile. (**A**) Pretreatment CT image at the true cord level shows involvement of the entire right cord, which is a paramedian position. The ipsilateral paraglottic space is obliterated (large arrow), when compared to the contralateral side (small arrow). (**B**) CT image obtained 4 months post-RT at the same level. There is complete resolution of the tumor. The laryngeal tissues appear symmetric, and the paraglottic space on the right side has reappeared (arrow); post-RT CT-score 1. The patient is without evidence of disease 31 months after completion of radiotherapy. Figure 1A, reprinted with permission.[10]

least one follow-up CT study between 1 and 6 months post-RT. For each patient, the first CT study post-RT was used for analysis. In some patients, this CT study was planned as part of their follow-up, in others it was performed because of some symptomatology, potentially reflecting local failure. Because no strict CT-based follow-up regimen was followed the patients were entered in a nonconsecutive way. All patients were followed-up clinically for at least 2 years after completion of RT. No patient was lost to follow-up.

Pre- and posttreatment CT studies were performed during intravenous contrast injection; 3-mm-thick contiguous sections were obtained with the plane of section parallel to the true vocal cords; field of view = 12 - 18cm, matrix: 512 x 512.[17] Before 1986, some studies were done with 5-mm-thick slices.

All CT studies were retrospectively reviewed by two of the authors who were unaware of patient outcome. Consensus was reached between the two reviewers for each CT study.

On pretreatment CT examination, each tumor was assigned a high- or low-risk profile for local failure after RT, based on previously determined specific CT parameters. T3 glottic tumors were considered to be at high risk if the tumor

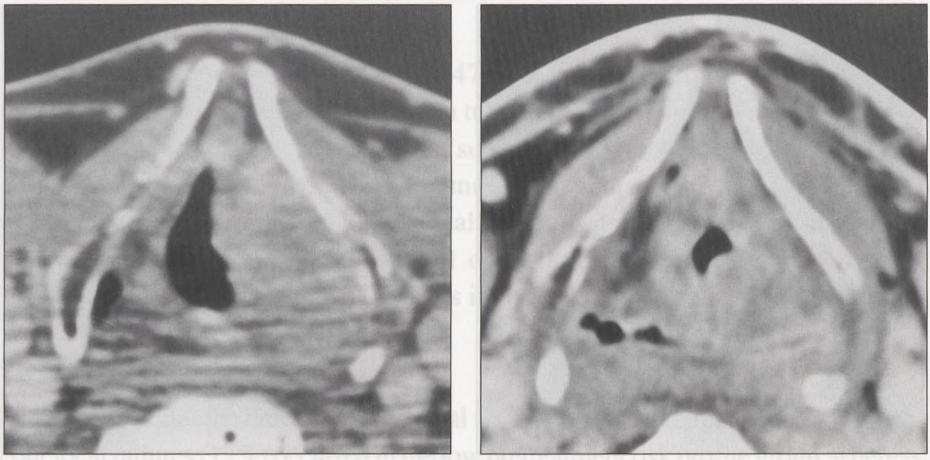

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FIGURE 2. CT images of a patient with a T3 supraglottic carcinoma and a low pretreatment risk profile. (**A**) Pretreatment CT image: tumor is seen in region of left false cord and paraglottic space. (**B**) CT image obtained at 2.5 months after radiotherapy. Tumor has regressed, but there is asymmetric obliteration of the fatty tissue at the left side, without obvious focal mass. Post-RT CT-score 2. The patient developed a local failure at 6 months post-RT, which was successfully treated by salvage laryngectomy.

volume was > 3.5 cm^3, or if a tumor with lower volume showed associated sclerosis of more than one laryngeal cartilage: the ipsilateral arytenoid and adjacent part of the cricoid cartilage.[8,10] A high-risk profile was attributed to a supraglottic tumor if its tumor volume was > 6 cm^3.[7,11] In 3 patients the pretreatment CT study was not available; categorization into high- or low-risk profile was done in these patients by reviewing the report previously made by one of the authors (AAM). Determination of the risk profile in the patient who received neoadjuvant chemotherapy was based on a CT scan before initiation of chemotherapy.

The post-RT CT examinations were evaluated for post-RT changes using a three-point post-RT CT-score: 1 = expected post-RT changes: complete resolution of the tumor at the primary site and symmetrically appearing laryngeal and hypopharyngeal tissues (Figure 1); 2 = focal mass with a maximal diameter of < 1 cm and/or asymmetric obliteration of laryngeal tissue planes (Figure 2); 3 = focal mass with a maximal diameter of > 1 cm, or < 50 % estimated tumor volume reduction (Figure 3). When a post-RT CT study demonstrated a focal mass, both the largest and the second-largest dimension perpendicular to the first were determined in millimeters. If both dimensions were < 1 cm, the mass was classified as post-RT CT-score 2. If one (or two) dimensions exceeded 1 cm, the lesion was classified as post-RT CT-score 3. According to preliminary experience,[6] this post-

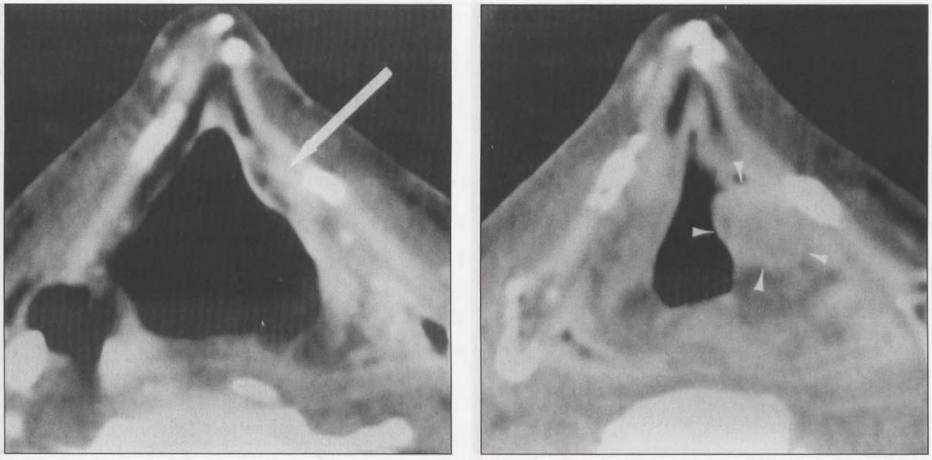

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FIGURE 3. CT images of a patient with a T3 carcinoma of the left true vocal cord and a high pretreatment risk profile. **A**. Pretreatment CT image just above the false cord level demonstrates involvement of the left aryepiglottic fold and obliteration of the paraglottic space (arrows). **B**. CT image at the same level, obtained at 3 months post-RT. A focal mass, in the left aryepiglottic fold, with a maximal diameter slightly over 1 cm (arrowheads) has developed; post-RT CT-score 3. Salvage laryngectomy confirmed the presence of local recurrence. The patient is alive without evidence of disease 2 years, 3 months after the operation. Figure 3A, reprinted with permission.[10]

RT CT-scoring system can be interpreted as: 1 = likely to achieve permanent local control; 2 = indeterminate; 3 = suspicious for local failure.

In 5 patients, the follow-up examination was not available for review. In these cases determination of the post-RT CT-score was done by reviewing the report previously made by one of the investigators (AAM).

The endpoint used in the statistical analysis was time to local failure (loss of laryngeal function), either due to local recurrence or chondronecrosis resulting in laryngectomy or permanent tracheostomy.

Statistical methods

Kaplan-Meier techniques were used to estimate local failure-free probabilities and to draw survival curves based on either pretreatment risk profile or post-RT CT-score groups. Differences between pretreatment risk profiles and post-RT CT-score groups were tested by means of log-rank tests. Calculation of risk ratios and simultaneous testing of pretreatment risk profile and post-RT CT-scores were performed by Cox proportional hazard analysis. All analyses were performed with SAS statistical software (V6.12).

RESULTS

At a median follow-up of 4 years, 28 (47%) local failures were detected. Local failure was due to pathologically-proven tumor recurrence in 22 patients (37%); 5 patients underwent total laryngectomy for suspected recurrence, or laryngeal necrosis and no tumor was found in the specimen; 1 patient died suddenly in severe respiratory distress, attributed to laryngeal chondronecrosis. Mean time to the first post-RT CT study was 91 days (SD, 41 days; range 1-6 months) and similar in both pretreatment risk groups, as well as in the three post-RT CT-score groups.

Pre-RT risk profile and local failure

Figure 4 illustrates the time interval to local failure based on pretreatment risk profile. Four local failures (17%) occurred in the low pretreatment risk profile group, whereas 24 patients (69%) developed a local failure in the high pretreatment risk profile group. At 2 years, the local control rate was 88% in the low pretreatment risk profile group (95% CI: 66 - 96%), and 34% (95% CI: 19 - 50%) in the high pretreatment risk profile group. This difference was statistically highly significant (risk ratio 6.583; 95% CI: 2.265 - 9.129; $p = 0.0001$).

Post-RT score and local failure

Figure 5 illustrates the time interval to local failure based on post-RT CT-score. One of 18 patients with post-RT CT-score 1 failed locally. This patient had a high-risk pretreatment profile and underwent laryngectomy 19 months after completion of therapy due to laryngeal chondronecrosis. In a group of 21 patients with post-RT CT-score 2, 9 patients failed locally. In the group of patients with post-RT CT-score 3, 18 of 20 patients failed locally. The local control rates at two years were 94% for score 1 (95% CI: 67 - 99%), 67% for score 2 (95% CI: 43 - 83%) and 10% for score 3 (95% CI: 2 - 27%). This also proved to be highly significantly different (risk ratio 4.760; 95% CI: 2.278 - 9.950; $p = 0.0001$).

Combination of pre-RT risk profile and post-RT CT-score

Figure 6A illustrates the time interval to local failure for the different post-RT CT-scores within the group of patients with a low pretreatment risk profile ($n = 24$). In a group of 14 patients with score 1 there were no local failures, whereas 2 patients with score 3 both failed locally. In the group with score 2 ($n = 8$), the number of local failures was 2. Local control rates at 2 years for patients with a low pretreatment risk profile were 100% for score 1, 88% for score 2 and 0% for score 3.

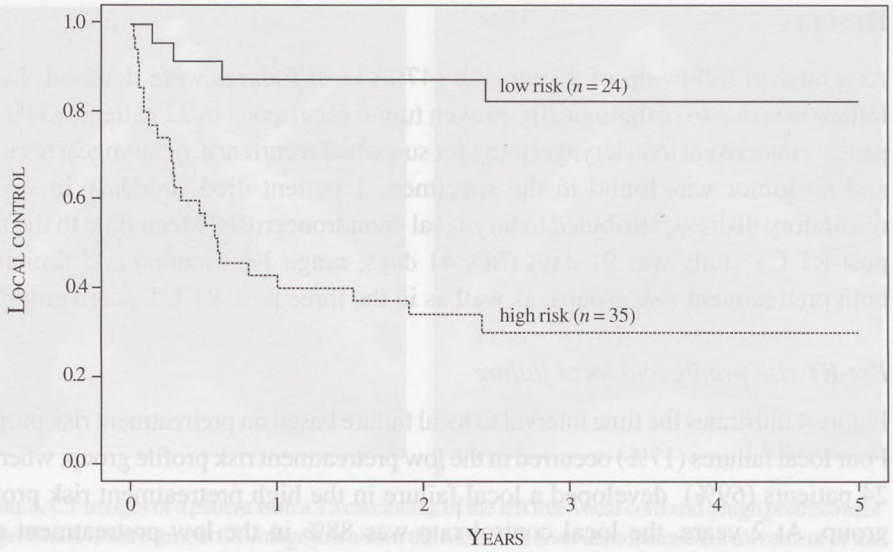

FIGURE 4. Local control after radiotherapy for patients with different pretreatment imaging risk profiles ($n = 59$).

Figure 6B illustrates the time interval to local failure for the different post-RT CT-scores within the group of patients with a high pretreatment risk profile ($n = 35$). One of 4 patients with a post-RT CT-score 1 failed locally, whereas for 18 patients with post-RT CT-score 3, the number of local failures was 16. In the group with post-RT CT-score 2 ($n = 13$), the number of local failures was 7. Local control rates at 2 years for patients with a high pretreatment risk profile were 75%, 54% and 11%, respectively.

Analyzing both parameters in a Cox proportional hazard analysis revealed that post-RT CT-score was a better prognosticator than the pretreatment CT risk profile classification.

DISCUSSION

In this study, the predictive value of CT-based pretreatment risk profiles, as well as a post-RT CT-scoring system, for the likelihood of local failure after definitive RT in a group of patients with laryngeal carcinoma have been tested. This study updates the preliminary experience from our institution concerning the expected post-RT changes and primary site response of the irradiated larynx.[5,6]

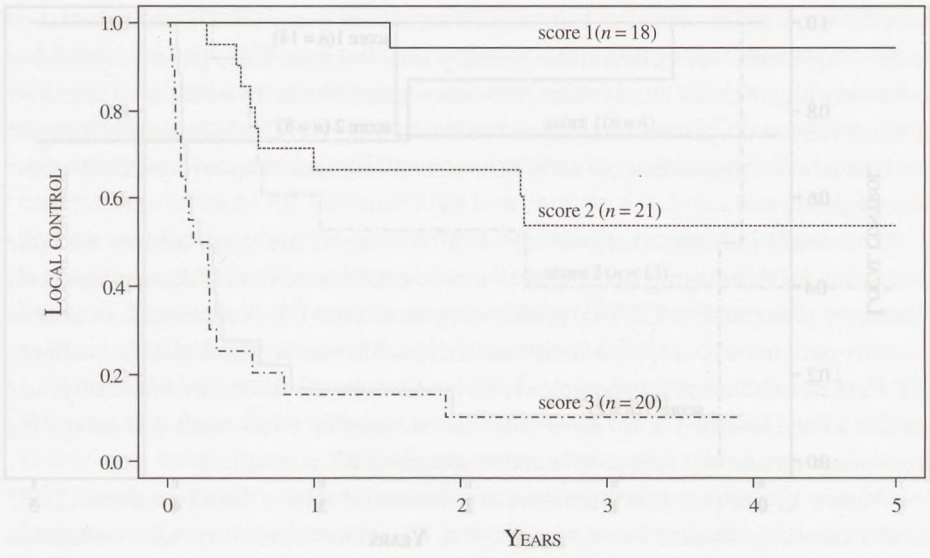

FIGURE 5. Local control after radiotherapy for patients with different post-RT CT-scores ($n = 59$).

Predictive value of CT-based pretreatment risk profiles

Previous reports from our group suggest that patients irradiated for a laryngeal carcinoma can be stratified in different risk groups for primary site failure based on pretreatment CT studies.[7,8,10,11] In these reports, risk profiles based on pre-RT CT-imaging criteria are presented for supraglottic (T1-T4) and glottic (T3) carcinomas. These pre-RT risk profiles were applied to our study population, without taking into account the post-RT evaluation (Figure 4). As expected, the obtained risk profiles very well differentiated between patients with a high risk and those with a low risk of developing a local failure.

A recent study suggested criteria for separating routine postradiation changes from significant focal masses using post-RT CT studies.[5,6] This post-RT CT-scoring system was applied to our patient group, without taking into account the pre-RT evaluation (Figure 5). The results of this study show that patients irradiated for a laryngeal carcinoma can also be grouped in three risk groups for primary site failure based on posttreatment CT studies.

Post-RT CT-score 1 (expected tissue changes after RT) is a very strong predictor of local control. Only 1 of 18 patients with score 1 failed locally, and this failure was due to a treatment-related complication (laryngeal necrosis).

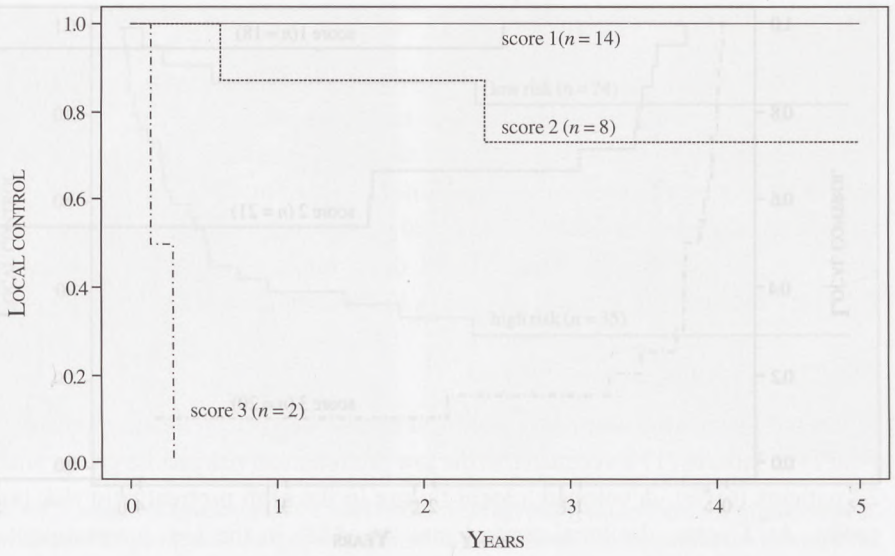

FIGURE 6A. Local control after radiotherapy for patients with different post-RT CT-scores. Patients with a low pretreatment imaging risk profile ($n = 24$).

Patients with score 3 do very poorly; almost all these patients will develop a local failure. Only 2 of 20 patients in the score 3 group remained continuously free of disease at the primary site. Both of these patients had a persistent focal mass on the final follow-up CT. In the first patient, this mass lesion could be explained by focal fibrosis, while in the second patient the lesion could be explained by enhancing tissue around the ventricular saccule, probably the result of chronic inflammation. Despite these two false-positive cases, our findings strongly suggest that further exploration in these post-RT CT-score 3 patients is warranted, even though deep biopsies could aggravate or initiate necrosis.[18] Fluorodeoxyglucose (FDG) or thallium-imaging may prove to be a useful intermediate step in cases where biopsy is considered too risky. Ongoing studies suggest that radionuclide imaging can detect local recurrences with a higher accuracy than purely anatomically-based methods, such as CT and magnetic resonance imaging (MRI).[19-24]

The local outcome of patients classified as post-RT CT-score 2 is indeterminate. Around 40% of these patients developed a local recurrence. This indicates that these patients remain at a relatively high risk for local failure. Therefore, these patients should be intensively followed-up clinically. In our institution, this group of patients is also followed-up by "CT surveillance"; after obtaining a "base-line" CT, 3 to 4 months post-RT, the CT examination is repeated at 4-months intervals for a minimum of 2 years, to detect local failure as early as possible.

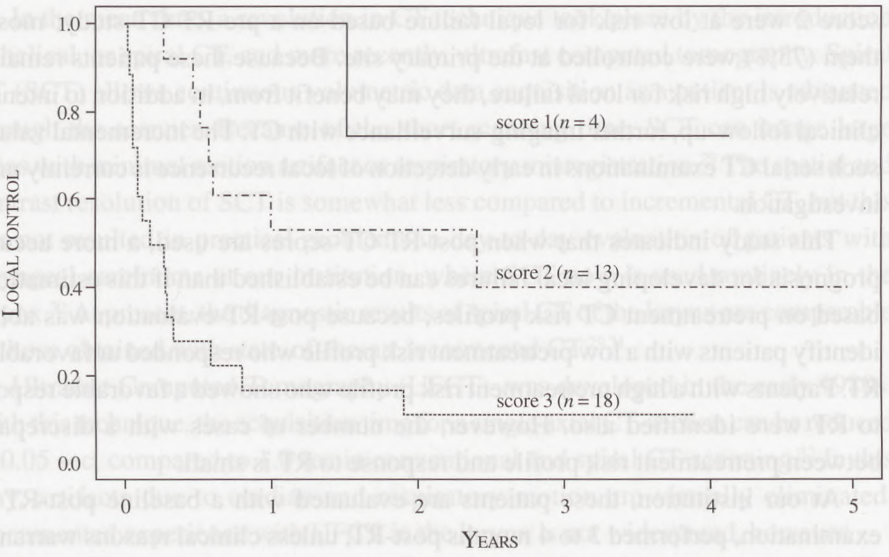

FIGURE 6B. Local control after radiotherapy for patients with different post-RT CT-scores. Patients with a high pretreatment imaging risk profile ($n = 35$).

Use of the post-RT CT-scoring system within the two pretreatment risk groups resulted in an additional separation within both groups into three risk groups for local recurrence (Figure 6). In patients with a low pretreatment risk profile, classification into the post-RT CT-score 1 group was an infallible sign of local control (Figure 6A). Patients with a high pretreatment risk profile, but with a favorable response to RT, could also be identified (Figure 6B). Only 1 of 4 patients, classified as high risk on pre-RT CT, failed locally when classified as score 1 on the post-RT CT scan, and this failure was due to laryngeal necrosis. These findings suggest that in the score 1 group, additional CT follow-up is not necessary, unless there is clinical suspicion of recurrence.

Patients classified as post-RT CT-score 3 have a very high risk of developing a local recurrence. Most patients in this group belonged, as could be expected, to the high pretreatment risk profile group. Interestingly, some poor responders identified by follow-up CT initially had a low risk pretreatment CT profile; the poor response in these patients could be due to an aggressive tumor biology and/or inherent insensitivity to irradiation. These lesions might also have taken advantage of a suboptimal tumor-host interaction, such as a compromised immune status.

The patients in the post-RT CT-score 2 category ($n = 21$) show an intermediate risk of local recurrence. About 60% of the patients in this group belonged to the pre-RT high risk group, and half of them failed locally. About 40% of patients with

score 2 were at low risk for local failure based on a pre-RT CT study; most of them (75%) were controlled at the primary site. Because these patients remain at relatively high risk for local failure, they may benefit from, in addition to intensive clinical follow-up, further imaging-surveillance with CT. The incremental value of such serial CT examinations in early detection of local recurrence is currently under investigation.

This study indicates that when post-RT CT-scores are used, a more accurate prognosis for developing local failures can be established than if this estimation is based on pretreatment CT risk profiles, because post-RT evaluation was able to identify patients with a low pretreatment risk profile who responded unfavorably to RT. Patients with a high pretreatment risk profile who showed a favorable response to RT were identified also. However, the number of cases with a discrepancy between pretreatment risk profile and response to RT is small.

At our institution, these patients are evaluated with a baseline post-RT CT examination, performed 3 to 4 months post-RT, unless clinical reasons warrant an earlier study. This approach is supported by data from FDG-positron emission tomography (PET) studies, showing that baseline exams before 4 months post-RT may not accurately reflect outcome and that studies done at 4 months and later result in a more accurate prediction of outcome.[25,26] Use of this imaging-based information could potentially lead to more prompt salvage surgery. If this results in a survival benefit for these patients remains subject of further prospective study.

Pretreatment imaging, either CT or MRI, has become essential for the correct pretherapeutic staging and proper treatment of these tumors.[27,28] Pretreatment risk profile determination can help in treatment selection.[10,11] At our institution, pre-RT imaging risk profiles are also used to insure a more accurate informed consent process when the relative value of surgery and radiotherapy for the likelihood of local failure are being discussed with the patient. In this approach, pretreatment risk profile determination is an integrated part of the imaging evaluation that is already performed as part of the staging procedure.

In this retrospective study (1980 - 1993) a "conventional" dynamic incremental CT technique was used to image the larynx. At present, one might consider using MRI due to the multiplanar imaging capabilities and the high soft-tissue detail. The question which modality, CT or MRI, is the method of choice in imaging of the (post-RT) larynx has not yet been answered definitively. This is still an on-going debate. In a recent paper on laryngeal staging, no significant difference was demonstrated between MRI and CT , both combined with clinical evaluation.[27,28] To our knowledge, no studies comparing CT and MRI for evaluation of the larynx after radiation treatment are available.

In the mean time, a revolution in CT technique took place by the introduction of helical, or spiral CT, and more recently, ultrafast computed tomography. Spiral CT (SCT) allows continuous volumetric data acquisition as a patient is advanced through the scanner. Because of the short scanning time, SCT can image large areas with minimal motion artifact or respiratory misregistration.[29] The spatial and contrast resolution of SCT is somewhat less compared to incremental CT, but this has not resulted in practical problems in day-to-day evaluation of patients with laryngeal carcinoma at our institution, where SCT now is used routinely in the larynx.[30] At present, the diagnostic results of spiral CT of the larynx are comparable to those obtained with state-of-the-art incremental CT.[29,31]

Ultrafast Computed Tomography (UFCT) was developed in the early 1980s. With this technique, the acquisition time for a single axial CT-section can be reduced to 0.05 sec, compared to 1.0 sec in conventional and spiral CT-scanning.[32] In this way, artifacts due to cardiac and respiratory motion are virtually eliminated. Documented experience with UFCT in the larynx is not widespread, however.

In the present study, we have not collected data on intra/inter-observer variability of using the post-RT CT-scoring system. Recently, data on intra- and interobserver reproducibility of CT interpretation of laryngeal carcinoma were reported.[33] Moderate to substantial intraobserver reproducibility was found for most structures examined. Fair to substantial reproducibility was demonstrated for interobserver variability. They conclude that "Categorization of patterns or degrees of involvement can be done within acceptable limits of variability, allowing the construction of tumor scores based on anatomic tumor extent, if the image interpretation is done by the same (experienced) observer". Our study set-up meets this requirement, because all CT studies were reviewed in consensus by two observers, one of whom is an experienced head and neck radiologist (AAM).

CONCLUSION

Pretreatment CT risk profiles, as well as posttreatment CT evaluation can identify patients with laryngeal carcinomas at high risk for developing local failure. When the post-RT CT-score is available, it proves to be an even better prognosticator than the pretreatment CT risk profile.

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CHAPTER 7

General discussion and future perspectives

GENERAL DISCUSSION

The studies described in this thesis were undertaken to investigate the possibilities of pre- and post-radiotherapy (RT) Computed Tomography (CT) in the evaluation of the primary site in patients with laryngeal and hypopharyngeal cancer, and to determine which imaging parameters can be used as predictors of local control after definitive RT. Various earlier reports identified the volume of the primary lesion as measured on pretreatment *imaging* (CT) studies as a significant predictor of local control.[1-4] To date, the Tumor Node Metastasis (TNM) classification system, which is traditionally based on endoscopic and other *clinical* findings, has been the most frequently used method for categorizing patients into different stage groups, with differences in prognosis and corresponding therapeutic options. As a first approach we have shown that T3-staged tumors of the head and neck show considerable variability in tumor volumes *(Chapter 2)*. Thus, the current TNM-staging system is unable to group head and neck tumors of the same volumetric range into the same (T3) stage. The prognostic value of the TNM classification may be enhanced by incorporation of tumor volume data.

We next investigated whether pretreatment CT can predict local control in patients with squamous cell carcinoma of different laryngeal and hypopharyngeal subsites, that were treated with RT alone. For all investigated sites; T3 glottic larynx carcinoma, T1/T2 pyriform sinus carcinoma and supraglottic carcinoma, pretreatment CT parameters could stratify patients into those in whom permanent control at the primary site is very likely (favorable), and those in whom it is much less likely (unfavorable) *(Chapters 3-5)*.

Finally, in the third part of this thesis we assessed the value of post-RT CT findings for prediction of local control in laryngeal cancer. Post-RT CT evaluation proved to be an even better prognosticator than pretreatment CT parameters *(Chapter 6)*.

Tumor volume delineation and measurement

If tumor volume is to be used as an addition to the TNM classification system, its measurement must be operationally feasible and reproducible. The technique needed to measure tumor volume is simple, short, and inexpensive. The summation-of-areas technique, used in this thesis, has previously been shown to be accurate within 5 to 10% of the actual tumor volume.[5-7] Knowledge of normal anatomy is required, as well as an understanding of the spread pattern of laryngeal and hypopharyngeal cancer. When peritumoral edema is present, it is often impossible

to precisely define the margin of the cancer. Therefore, to ensure reproducibility, no attempt should be made to differentiate between tumor and edema *(Chapters 2 - 5)*. Although there will be a component of the apparent 'tumor volume' that represents edema, and will artificially inflate the calculated tumor volume, we believe that this method nevertheless gives the most consistent results.

Recently, Hermans et al. demonstrated that the interpretation of CT images of laryngeal cancer is reproducible within and between observers.[8] They found that categorization of patterns or degrees of involvement can be done within acceptable limits of variability, allowing the construction of tumor scores based on anatomic tumor extent. Total variability in CT-based tumor volume measurements can be reduced by having the measurements done by a single trained observer.[9]

Our studies *(Chapters 2-5)* and many others have shown that, for all subsites in the head and neck, CT-based tumor volume measurements can be performed on a routine basis.[1-4,9-13] Prerequisites remain good-quality images and an appropriate work station or digitizer.

Value of pre-RT CT as a predictor of local control in T3 glottic, T1/T2 pyriform sinus and supraglottic carcinoma

In current clinical practice the patient with a laryngeal or hypopharyngeal carcinoma treated with RT is confronted with local control rates, as measured in large cohorts of similar staged cases and published in the literature (influenced by local treatment resources and experience). The studies described in *Chapter 3-5* are based on patient material from the University of Florida (UFL). Local control rates reported previously from UFL for the subsites we investigated are the following: T3 glottic carcinoma: ±60%; T1/T2 pyriform carcinoma: ±80%; T2/T3 supraglottic carcinoma: ±75%.[14-16]

We have demonstrated, using comparable patient material, that pretreatment CT parameters can stratify patients with T3 glottic carcinoma *(Chapter 3)*, T1/T2 pyriform sinus carcinoma *(Chapter 4)* and supraglottic carcinoma *(Chapter 5)* into those likely (> 80%) and those much less likely (< 40%) to be locally controlled with definitive RT. In these retrospective studies, local control rates could have been improved by using a CT-risk profile, including parameters such as tumor volume, involvement of specific sites and cartilage abnormalities. No other parameter provided additional significant information regarding the probability of local control when considered simultaneously with volume. For each site we were able to identify a 'threshold' volume above which primary site prognosis diminished considerably.

These data may lead to an individualized estimate of the chances of local control, ensuring a more accurate informed consent process when the relative value of surgery and RT for likelihood of local control are being discussed with the patient.

Recently, a comparable retrospective study on 119 patients with glottic squamous cell carcinoma (T1, $n = 61$; T2, $n = 40$; T3, $n = 14$; T4, $n = 4$) who were treated with RT was published by Hermans et al.[11] Overall, the results of this study corroborate well with our findings. Failure probability analysis showed a clear relation between larger glottic tumor volume and increasing risk of local failure. Surprisingly, in a multivariate analysis, tumor volume was not found to be an independent predictor of local outcome (neither was T-stage). The degree of involvement of laryngeal deep tissues was found to be the statistically independent predictor of local outcome. While our series consisted of 42 patients with T3 glottic carcinoma, the series of Hermans et al. consisted mainly of T1 and T2 glottic tumors. They could not examine the possible correlation between tumor volume and local control for the T3 (and T4) categories because of the limited number of patients within these categories. This underscores the problem of comparability between studies of this kind in the head and neck.

The threshold volume of 3.5 cm^3 found in T3 glottic carcinoma *(Chapter 3)* is considerably different from the critical volume suggested of 6.5 cm^3 for pyriform sinus *(Chapter 4)* and 6.0 cm^3 for supraglottic tumors *(Chapter 5)*. The reason for this difference is not completely understood. One reason for the lower critical volume for a glottic carcinoma might be anatomical, and related to cricoarytenoid joint invasion. A glottic tumor is intimately related to the arytenoid, cricoid and thyroid cartilages, and may therefore cause occult cartilage invasion, with its inherent decrease in radiocurability, at a much lower volume than a pyriform sinus or supraglottic carcinoma.

At all sites studied, we found a few high-volume lesions that were locally controlled, and some low-volume tumors in which local control failed. There seem to be factors that cause primary site failure which cannot be explained on the basis of patho-anatomic extent, tumor volume, or a combination of the two. This is probably due to more biologically aggressive tumors or tumor-host interactions that are not yet fully understood. Identification of biological markers might help to define the small group of patients who are likely to fail, despite having lesions which appear to be favorable for cure on the basis of current clinical-diagnostic evaluation. Although implementation of volume data seems to have gained a role in multidisciplinary treatment planning of head and neck cancer patients, it cannot be used as an isolated criterion to decide the treatment for any individual patient.

Value of post-RT CT as a predictor of local control in laryngeal cancer

After RT, residual or recurrent tumor can be difficult to detect by physical examination because of varying degrees of edema and fibrosis. However, early detection of recurrence is crucial if salvage therapy is to be initiated.

Chapter 6 describes the results of a study in which we tested the predictive value of a post-RT CT-scoring system. Post-RT CT examinations were evaluated for posttreatment changes using a three-point post-RT CT-score: 1 = expected post-RT changes; 2 = focal mass with a maximal diameter of < 1 cm and/or asymmetric obliteration of laryngeal tissue planes; 3 = focal mass with a maximal diameter of > 1 cm, or < 50% estimated tumor volume reduction. The different post-RT CT-scores were interpreted as follows: 1 = likely to achieve permanent local control; 2 = indeterminate; 3 = suspicious for local failure. The post-RT CT-scoring system was able to identify patients, irradiated for laryngeal carcinomas, at high risk of developing local failure. When the post-RT CT-score is available, it proves to be an even better prognosticator than the pretreatment CT-determined risk profiles. This is because the post-RT scoring system reflects the actual tumor response to irradiation, making it able to identify tumors with a discrepancy between pretreatment risk profile and RT-response.

The post-RT scoring system is based on a CT study ('baseline' CT), performed 3 to 4 months post-RT (unless clinical reasons warrant an earlier study). The choice of interval between RT and the baseline study is supported by data from FDG-positron emission tomography (PET) studies, showing that exams before 4 months post RT may not accurately reflect outcome and that such studies, done at 4 months and later result in a more accurate prediction of outcome.[17,18]

If the result of the baseline CT is post-RT CT-score 1 (likely to achieve permanent local control) additional CT follow-up is not necessary. This may result in cost reductions by eliminating further imaging studies, and possibly diminishing the frequency of clinical follow-up. In patients with a post-RT CT-score 3 (suspicious for local failure) immediate further investigation under general anesthesia seems warranted, as the likelihood of local failure is high. If indicated, post-irradiation biopsies should be performed with caution, since the capacity of the irradiated tissue to recover is diminished. The local outcome of patients classified as post-RT CT-score 2 is indeterminate. Around 40% of these patients developed a local recurrence, indicating that this patient category remains at a relatively high risk for local failure. Therefore, these patients should be intensively followed-up clinically, as well as with imaging. At the University of Florida, this group of patients is followed-up by 'CT surveillance': after obtaining a 'baseline' CT, three to four

months post-RT, the CT examination is repeated at four-month intervals for a minimum of two years so that local failure can be detected as early as possible. Use of this imaging-based information could potentially lead to more prompt salvage surgery. Whether this results in a survival benefit for these patients remains the subject of further prospective study.

FUTURE PERSPECTIVES

To date, many *retrospective* studies have shown that imaging parameters identified on CT and MRI studies may predict the local outcome of patients with laryngeal carcinoma treated with definitive RT.[1,3,4,11,12,19,20] Imaging parameters that were identified as risk factors included the involvement of specific sites, depending on the location of the primary tumor, cartilage abnormalities and tumor volume. In *Chapters 3 and 4* the concept of a CT-based risk profile was introduced for T3 glottic and T1/T2 pyriform sinus carcinoma, respectively. By combining various parameters, informative risk groups based on imaging criteria were created with what can be characterized as low, moderate and high risk for local failure.

The studies described in *Chapters 3-6* provide a foundation for future investigations that should attempt to determine the accuracy of imaging risk profiles. *Prospective* confirmation, preferably in multiple centers, and further refinements of these imaging profiles may have a direct influence on stratification of patients for organ preservation therapy. In the future, the final decision to treat patients with nonsurgical therapy may be based on the predicted chance of local control as determined by the individual imaging risk profile.

Patients with a favorable (low-risk) imaging profile will be suitable candidates for unimodality treatment (RT). For patients with an unfavorable (high-risk) imaging profile, surgical resection could remain the most appropriate treatment. If such patients elect to proceed with RT they are considered at high risk (> 50%) for failure at the primary site. In addition to frequent clinical follow-up, these patients may benefit from 'CT surveillance' *(Chapter 6)*. The incremental value of such serial CT examinations in detecting recurrence, while it is still curable by salvage surgery, needs to be investigated.

Development of imaging profiles that may predict outcome will expand the role of imaging in the management of head and neck cancer. Further refinements may allow integration of specific imaging parameters into staging systems. For example, tumor volume can be considered as a refinement of the T-category in the TNM staging system of laryngeal cancer. Future investigations should preferably report separate results on separate sites (and T-stages). Too often, published series mix

different anatomic subsites and clinical situations. For example, glottic and supraglottic tumors should not be considered together, as the anatomic situation (and hence the natural history) is different.

If the findings reported in *Chapters 3-5* and previous similar studies are corroborated by other investigators, tumor volume and site-specific parameters such as cartilage abnormalities and involvement of certain sites may become part of the staging classification for laryngeal carcinoma. Some effort should be made to begin to integrate significant imaging parameters, such as tumor volume, into the system of end result reporting.

Although both CT and MRI continue to improve, the largest area of potential growth in head and neck imaging will likely come from the integration of metabolic and functional imaging techniques.[21] Progress may be expected in the differentiation between recurrent tumor versus posttreatment changes. The study described in *Chapter 6* suggests CT-based morphological criteria for separating routine postradiation changes from significant focal masses. Tissue characterization using dynamic MRI might become important in the future. Dynamic MRI is a contrast-enhanced MR-technique showing progression of enhancement over time in a lesion. This technique has already been applied in other parts of the body.[22,23] Preliminary reports on the role of dynamic MRI imaging in the head and neck seem promising.[24,25] Another potential application might be MR spectroscopy. Because MR spectroscopy is based on the chemical composition of a tissue rather than anatomic landmarks, this technique has potential to enable evaluation of lesions in a manner not possible with CT or MR imaging. Mukherji et al. have reported preliminary findings with this technique in the head and neck.[26,27]

Metabolic imaging with radionuclides, including positron emission tomography (PET) and single photon emission computed tomography (SPECT), is an area of active investigation in head and neck imaging.[17,18,28-32] Studies that define the role of these different techniques should be encouraged as part of a multidisciplinary team approach to solve this often difficult clinical problem.

To sum up, the anatomic information available from imaging needs to be combined with volumetric and tumor biology data to allow for the most accurate pretreatment assessment of head and neck cancer. In the future, this analysis will likely provide the most rational basis for clinical decision making when combined with patient preference and available treatment resources and experience. There is no doubt that this effort should be a multidisciplinary one. No single discipline has all of the answers. The amount of information available across disciplines is insurmountable for a single individual. A combination of human and technological teamwork is the best way to put the collective base of knowledge and experience to practice.

This thesis fits well into the framework outlined by Bailey[33], who addressed optimal management and patient prognosis in the individual case of head and neck cancer. He visualized the possibility of a mathemathical formula with dozens of variables pertaining to the visible characteristics of the tumor *(Chapter 3-5)*, the standard assessment of the patient *(Chapter 2)*, new parameters of tumor biology and host response, the impact of therapy *(Chapter 6)*, and additional information gathered from the surgical specimen. Over time, these factors must be weighted according to their predictive importance (as additional information is gained).

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CHAPTER 8

Summary

The studies described in this thesis were undertaken to investigate the possibilities of pre- and post-radiotherapy (RT) Computed Tomography (CT) in the evaluation of the primary site in patients with laryngeal and hypopharyngeal cancer, and to determine which imaging parameters can be used as predictors of local control after definitive RT.

Chapter 1 includes a short introduction to laryngeal and hypopharyngeal cancer and describes the aims of the thesis. Surgery and/or RT are curative treatment options for patients with cancer of the larynx or hypopharynx. The choice between these two options presents a dilemma. In surgery, the tumor is removed, including the entire larynx. As a consequence, the patient is cured of his/her cancer with the loss of his/her natural voice. Radiotherapy allows for preservation of laryngeal function, including the voice. However, if RT fails and a local recurrence develops the patient has endured a five-to seven-weeks course of (unnecessary) high-dose RT. Surgical salvage, which is then the only therapeutic option left, will still result in the loss of voice.

In current clinical practice the patient with a laryngeal or hypopharyngeal carcinoma treated with RT is confronted with local control rates, as measured in large cohorts of similar TNM [1] staged cases. More 'individualized' selection of patients who are likely to be cured with definitive RT could reduce the fraction of patients undergoing salvage surgery and may improve local control rates. Earlier studies have shown that the use of CT can be potentially useful in this selection process.

Chapter 2 describes a study on variability of tumor volumes in T3 staged head and neck tumors. In addition, a technique of CT-based tumor volume measurements (summation-of-areas technique) is described. Various reports in the literature have recognized a positive correlation between tumor volume and prognosis for all subsites of the head and neck. TNM parameters, in which the T-category describes the local extent of the primary tumor, are used to stratify patients into stage-groups with comparable prognosis. It might be assumed that the same stage-group would

[1] TNM: Clinically, head and neck tumors are staged by the TNM classifications developed by the American Joint Committee on Cancer and the International Union Against Cancer ("T" stands for primary tumor, "N" for regional lymph nodes, and "M" for metastasis). As in other parts of the body, the T-stage is used to describe the local extent of tumors in the various subsites of the head and neck (T1 - T4), the N-stage describes metastatic disease of the regional lymph nodes (N0 - N3) and the M-stage refers to the presence (M1) or absence (M0) of distant metastases.

contain tumors with comparable volumes. Ideally, T-stage should be able to convey a clear understanding of tumor size. However, the TNM classification system describes head and neck tumors using anatomic or unidimensional criteria and may therefore fail to define the actual three-dimensional tumor bulk. To investigate this we measured variability of tumor volumes (**V**vol) in a group of 42 patients with T3 staged head and neck tumors. Following are the tumor volume measurements: T3 larynx carcinoma (n = 12) **V**vol, 1.7 - 17.0 cm^3 (median 3.7 cm^3); T3 oropharynx carcinoma (n = 13) **V**vol, 10.0 - 41.2 cm^3 (median 18.3 cm^3); T3 hypopharynx carcinoma (n = 10) **V**vol, 8.9 - 67.8 cm^3 (median 17.4 cm^3); T3 nasopharynx carcinoma (n = 3) **V**vol, 3.7 - 30.1 cm^3; T3 maxillary sinus carcinoma (n = 4) **V**vol, 56.0 - 103.1 cm^3. In each investigated site, we found that tumor volume variability was striking. From this study, we concluded that the current TNM system is unable to group tumors with comparable volumes into the same (T3) stage group. Incorporation of tumor volume data may lead to further refinement of the TNM classification.

In *Chapter 3* we assessed whether pretreatment CT can predict local control in patients with T3 squamous cell carcinoma of the glottic larynx treated with definitive RT. In 42 patients, tumor volumes and anatomic spread pattern were determined on pretreatment CT studies by consensus of two head and neck radiologists, who were blinded to patient outcome. Tumor volumes were calculated using the summation-of-areas technique. A tumor score, reflecting the anatomic spread pattern of the tumor as defined by involvement of 8 specific anatomical sites, was calculated for each primary lesion. Tumor scores, equal to the number of anatomic sites involved, ranged from 1 to 8. Sclerosis of the laryngeal cartilages (arytenoid and cricoid) adjacent to tumor was recorded. These CT parameters (tumor volume, tumor score and cartilage sclerosis) were correlated with local control. Local control for all patients in the study was 62%. Tumor volume was a significant predictor of local control. For tumors measuring < 3.5 cm^3 local control was achieved in 85% of patients, whereas for tumors ≥ 3.5 cm^3 local control was achieved in 25% of patients. Tumor score, as a measure of anatomic extent, was also found to be a significant predictor of local control. The local control rate for tumors assigned a low tumor score (≤ 5) was 78% as compared to 33% for tumors assigned a high tumor score (6, 7, or 8). A significant decrease in the local control rate was observed for cancers involving the paraglottic space at the false vocal cord level, the face of the arytenoid, and tumors involving the interarytenoid region. There were 12 patients with sclerosis of both the ipsilateral arytenoid and the adjacent cricoid cartilage.

These patients showed a marked decrease in local control. When tumor volume and cartilage sclerosis are combined, three imaging-based risk groups emerge from the study population with what can be characterized as low, moderate, and high risk for local failure. The local control rates in these low, moderate and high risk groups were 90%, 43% and 14%, respectively. No other parameter provided additional significant information regarding the probability of local control when considered simultaneously with tumor volume. In conclusion, pretreatment CT can stratify patients with T3 glottic carcinoma into groups more or less likely to be locally controlled with definitive RT. The ideal CT profile for a radiocurable T3 glottic larynx carcinoma is volume < 3.5 cm^3 and no or single laryngeal cartilage sclerosis. The local control rate achieved for such a CT favorable glottic lesion in this study was 90%.

In *Chapter 4* we evaluated pretreatment CT as a predictor of local control in T1/T2 pyriform sinus carcinoma treated with definitive RT. In 23 patients, tumor volumes and anatomic spread pattern were determined on pretreatment CT studies by consensus of two head and neck radiologists, who were blinded to patient outcome. Tumor volumes were calculated using the summation-of-areas technique. A tumor score, reflecting the anatomic spread pattern of the tumor as defined by involvement of 8 specific anatomical sites, was calculated for each primary lesion. Radiographic evidence of pyriform sinus apex disease was also recorded separately. Sclerosis of the laryngeal cartilages (arytenoid and cricoid) adjacent to tumor was recorded. These CT parameters (tumor volume, tumor score and cartilage sclerosis) were correlated with local control. Local control for all patients in the study was 78%.Tumor volume was a significant predictor of local control. For tumors measuring < 6.5 cm^3 local control was achieved in 89% of patients, whereas for tumors ≥ 6.5 cm^3 local control was achieved in 25% of patients. Tumor score, as a measure of anatomic extent, was also found to be a significant predictor of local control. The local control rate was not influenced significantly by the presence of 'minimal' apex disease (< 10 mm) but decreased significantly when 'bulk' apex disease (≥ 10 mm) was present. Laryngeal cartilage sclerosis was not a significant predictor of local control. When tumor volume and apex disease are combined, three imaging-based risk groups emerge from the study population with what can be characterized as low, moderate, and high risk for local failure. The local control rates in these low, moderate and high risk groups were 94%, 50% and 0%, respectively. In summary, CT can stratify patients with T1/T2 pyriform sinus carcinoma into groups more or less likely to be locally controlled with definitive

RT. The ideal CT profile for a radiocurable T1/T2 pyriform sinus carcinoma is volume < 6.5 cm^3 and minimal or no apex disease. The local control rate achieved for such a CT favorable pyriform lesion in this study was 94%.

Chapter 5 determines the utility of pretreatment CT for predicting primary site control in patients with supraglottic squamous cell carcinoma treated with definitive RT. Pretreatment CT studies in 63 patients were reviewed. Local recurrence and treatment complications resulting in permanent loss of laryngeal function were documented. Tumor volume was calculated using a computer digitizer (summation-of-areas technique) and pre-epiglottic space spread was estimated. Local control for all patients in the study was 70%. Tumor volume was a significant predictor of local control. Local control in tumors measuring < 6 cm^3 was 89%, whereas for tumors ≥ 6 cm^3 local control was achieved in 52% of patients. The likelihood of maintaining laryngeal function also varied with tumor volume: < 6 cm^3 (89%) versus ≥ 6 cm^3 (40%). Greater than 25% of pre-epiglottic space involvement by tumor was associated with a reduced chance of saving the larynx. From this study, we concluded that pretreatment CT measurements of tumor volume permits stratification of patients with supraglottic carcinoma treated with RT alone (which allows preservation of laryngeal function) into groups in which local control is more likely and less likely. Pre-epiglottic space spread is not a contraindication to using RT as the primary treatment for supraglottic carcinoma.

In *Chapter 6* we assessed if pre- and/or posttreatment CT can predict local failure in patients with laryngeal carcinoma treated with definitive RT. The pre- and post-RT CT examinations of 59 patients (glottic carcinoma; n = 30, and supraglottic carcinoma; n = 29) were reviewed. Local control was defined as absence of primary tumor recurrence and a functioning larynx. On the pretreatment CT study each tumor was assigned a high or low risk profile for local failure after RT. The post-RT CT examinations were evaluated for posttreatment changes using a three-point post-RT CT-score; score 1 = expected post-RT changes; score 2 = focal mass with a maximal diameter of < 1cm and/or asymmetric obliteration of laryngeal tissue planes; score 3 = focal mass with a maximal diameter of > 1cm, or < 50% estimated tumor volume reduction. The different post-RT CT-scores were interpreted as follows; 1 = likely to achieve permanent local control; 2 = indeterminate; 3 = suspicious for local failure. The local control rates at two years post-RT based on pretreatment CT evaluation were 88% for low pretreatment risk profile patients and 34% for high pretreatment risk profile patients. Based on

posttreatment CT, the local control rates at two years post RT were 94% for score 1, 67% for score 2, and 10% for score 3. When the post-RT CT-scoring system was combined with the two pretreatment risk groups, this resulted in an additional separation within both groups into three risk groups for local recurrence. This made it possible to identify patients with a low pretreatment risk profile who responded unfavorably to RT. Patients with a high pretreatment risk profile who showed a favorable response to RT were identified also. Post-RT CT-score was a better prognosticator than the pretreatment risk profile classification. In summary, pretreatment CT risk profiles, as well as post-RT CT evaluation can identify patients, irradiated for laryngeal carcinomas, at high risk for developing local failure.

In *Chapter 7* the findings of this thesis and future developments are reviewed.

Samenvatting

De onderzoeken beschreven in dit proefschrift richten zich op de rol van computer tomografie (CT) voor en na radiotherapie (RT) bij het voorspellen van de kans op lokale tumorcontrole bij patiënten met kanker van de larynx en hypofarynx.

Hoofdstuk 1 betreft een korte introductie over larynx- en hypofarynxcarcinoom en beschrijft de afzonderlijke doelstellingen van het in dit proefschrift verrichte onderzoek. Chirurgie en/of RT zijn curatieve behandelingsopties voor een patiënt met kanker van de larynx of hypofarynx. De keuze tussen deze twee behandelingen creëert een dilemma. Bij chirurgie wordt de tumor samen met de gehele larynx verwijderd. De patiënt is hierdoor genezen maar verliest als gevolg van de ingreep zijn/haar stem. Bij RT blijft de functie van de larynx, inclusief de stem, gespaard. Maar als de tumor ongunstig reageert op de bestraling en een lokaal recidief ontstaat, is de patiënt gedurende vijf tot zeven weken (onnodig) bestraald. De enige overgebleven behandelingsoptie is dan alsnog chirurgie, waarbij de stem verloren gaat.

In de dagelijkse praktijk wordt een patiënt met kanker van de larynx of hypofarynx die met RT behandeld wordt, geïnformeerd over de (te verwachten) lokale controle. Deze informatie wordt verkregen op basis van gegevens uit grote aantallen, identiek behandelde, patiënten met vergelijkbare TNM[1] stagering. Een meer 'geïndividualiseerde' selectie van patiënten die een hoge kans hebben op genezing met RT zou het aantal patiënten dat alsnog chirurgie moet ondergaan kunnen reduceren en de lokale controle kunnen verbeteren. Eerder uitgevoerde studies tonen aan dat het gebruik van CT mogelijk nuttig is bij dit selectie proces.

Hoofdstuk 2 beschrijft een studie naar variabiliteit van tumorvolume in een groep identiek (T3) gestageerde hoofd- halstumoren. Een techniek wordt beschreven voor het meten van tumorvolume met CT: de 'summation-of-areas' techniek. Diverse eerdere publicaties hebben een positieve correlatie beschreven tussen het volume van de primaire tumor en de prognose voor alle lokaties in het hoofd- halsgebied. TNM parameters, waarvan de T-categorie de lokale uitbreiding van de primaire tumor beschrijft, worden gebruikt om patiënten in te delen in stadia met een

[1] TNM: Hoofd- halstumoren worden klinisch gestageerd met het TNM classificatiesysteem ontwikkeld door de 'American Joint Committee on Cancer' en de 'International Union Against Cancer' ('T' staat voor primaire tumor, 'N' voor regionale lymfklieren, en 'M' voor metastasen). Net als in andere delen van het lichaam dient het T-stadium om de lokale uitbreiding van tumoren in het hoofd- halsgebied te beschrijven (T1 - T4), het N-stadium beschrijft metastasering naar de regionale lymfklieren (N0 - N3) en het M-stadium betreft de aanwezigheid (M1) of afwezigheid (M0) van metastasen op afstand.

vergelijkbare prognose. Het lijkt aannemelijk dat binnen één stadium tumoren voorkomen met vergelijkbaar tumorvolume. Idealiter zou uit het T-stadium een duidelijk begrip over het tumorvolume moeten volgen. Het TNM classificatiesysteem beschrijft hoofd- halstumoren volgens anatomische of unidimensionele criteria en zou daarom de werkelijke driedimensionale tumormassa onvoldoende kunnen definiëren. Dit is onderzocht door variabiliteit van tumorvolume (**V**vol) te meten in een groep van 42 patiënten met een T3 tumor van het hoofd- halsgebied. De resultaten waren als volgt: T3 larynx carcinoom (n = 12) **V**vol: 1,7 - 17,0 cm^3 (mediaan 3,7 cm^3); T3 orofarynx carcinoom (n = 13) **V**vol: 10,0 - 41,2 cm^3 (mediaan 18,3 cm^3); T3 hypofarynx carcinoom (n = 10) **V**vol: 8,9 - 67,8 cm^3 (mediaan 17,4 cm^3); T3 nasofarynx carcinoom (n = 3) **V**vol: 3,7 - 30,1 cm^3; T3 sinus maxillaris carcinoom (n = 4) **V**vol: 56,0 - 103,1 cm^3. Voor iedere lokatie werd een aanzienlijke variatie in tumorvolume gevonden. De conclusie van dit onderzoek was dat het huidige TNM systeem niet in staat is om tumoren met vergelijkbaar volume onder te brengen in hetzelfde (T3) stadium. Incorporatie van tumorvolume kan leiden tot een verfijning van het TNM classificatiesysteem.

In *Hoofdstuk 3* wordt onderzocht of pre-RT CT gebruikt kan worden om de kans op lokale tumorcontrole te voorspellen bij patiënten met een bestraald T3 glottisch larynx carcinoom. Bij 42 patiënten is het tumorvolume en de anatomische uitbreiding bepaald op basis van een pre-RT CT scan. Dit werd uitgevoerd door twee hoofd-halsradiologen die niet op de hoogte waren van het resultaat van de bestraling. Tumorvolumes werden berekend met de 'summation-of-areas' techniek. Voor iedere primaire tumor werd een tumorscore berekend die de anatomische uitbreiding weergeeft, gebaseerd op aanwezigheid van tumor op 8 specifieke anatomische lokaties in de larynx. Tumorscores, gelijk aan het aantal anatomische lokaties aangedaan door tumor, varieerden tussen 1 en 8. Sclerose van de laryngeale kraakbeentjes (arytenoid en cricoid) in de nabijheid van tumor werd geregistreerd. Deze CT parameters (tumorvolume, tumorscore en kraakbeensclerose) werden gecorreleerd met lokale controle. De lokale controle voor alle patiënten in deze studie bedroeg 62%. Tumorvolume bleek significant gerelateerd aan lokale controle. Voor tumoren < 3,5 cm^3 werd lokale controle bereikt in 85% van de patiënten, terwijl voor tumoren ≥ 3,5 cm^3 de lokale controle 25% was. Tumorscore als maat voor anatomische uitbreiding bleek ook significant gerelateerd aan lokale controle. Voor afwijkingen met een tumorscore ≤ 5 werd een lokale controle bereikt van 75%, vergeleken met 38% voor laesies met een tumor score > 6. Een significante daling van de lokale controle werd gevonden voor tumoren met uitbreiding naar de paraglottische ruimte op het niveau van de valse stemband, de antero-mediale zijde

van het arytenoid en naar het gebied tussen beide arytenoiden. Er waren 12 patiënten met gecombineerde sclerose van arytenoid en cricoid. De lokale controle bij deze patiënten was duidelijk verlaagd (33%). Bij combinatie van tumorvolume en kraakbeensclerose bleken er drie risicogroepen te ontstaan met een laag, gemiddeld en hoog risico op een lokaal recidief. De lokale controle in deze drie groepen bedroeg respectievelijk 90%, 43% en 14%. In combinatie met tumorvolume gaf géén van de bovengenoemde CT-parameters additionele informatie met betrekking tot de kans op het bereiken van lokale tumorcontrole. Geconcludeerd wordt dat patiënten met een T3 glottisch larynx carcinoom met pre-RT CT ingedeeld kunnen worden in groepen waarin het bereiken van lokale controle na RT meer en minder waarschijnlijk is. Het ideale risicoprofiel voor het radiocurabele T3 glottisch larynx carcinoom is volume < 3,5 cm^3 zonder gecombineerde sclerose van arytenoid en cricoid (lokale controle in deze studie 90%).

In *Hoofdstuk 4* wordt de rol onderzocht van pre-RT CT ter voorspelling van lokale tumorcontrole bij patiënten met T1/T2 sinus pyriformis carcinoom. Bij 23 patiënten is het tumorvolume en de lokale uitbreiding bepaald op basis van een pre-RT CT scan. Dit werd uitgevoerd door twee hoofd- halsradiologen die niet op de hoogte waren van het resultaat van de bestraling. Tumorvolume werd berekend met de 'summation-of-areas' techniek. Voor iedere primaire tumor werd een tumorscore berekend die de anatomische uitbreiding weergeeft, gebaseerd op aanwezigheid van tumor op 8 specifieke anatomische lokaties in de larynx en hypofarynx. Tumoruitbreiding in de apex sinus pyriformis werd gekwantificeerd. Sclerose van de laryngeale kraakbeentjes (arytenoid en cricoid) in de nabijheid van tumor werd geregistreerd. Deze CT parameters (tumorvolume, tumorscore en kraakbeensclerose) werden gecorreleerd met lokale controle. De lokale controle voor alle patiënten in deze studie bedroeg 78%. Tumorvolume was significant gerelateerd aan lokale controle. Voor tumoren < 6,5 cm^3 werd lokale controle bereikt in 89% van de patiënten, terwijl voor tumoren ≥ 6,5 cm^3 de lokale controle 25% was. Tumorscore als maat voor anatomische uitbreiding bleek ook significant gerelateerd aan lokale controle. Patiënten met 'minimal apex disease' (< 10 mm) hadden geen daling van de lokale controle, terwijl bij 'bulk apex disease' (≥ 10 mm) de lokale controle significant afnam. Patiënten met kraakbeensclerose hadden geen daling van de lokale controle. Bij combinatie van tumorvolume en tumoruitbreiding in de apex sinus pyriformis bleken er drie risicogroepen te ontstaan met een laag, gemiddeld en hoog risico op een lokaal recidief. De lokale controle in deze drie groepen bedroeg respectievelijk 94%, 50% en 0%. Geconcludeerd wordt dat patiënten met een T1/T2 sinus pyriformis carcinoom met pre-RT CT ingedeeld kunnen worden in groepen

waarin het bereiken van lokale controle na RT meer en minder waarschijnlijk is. Het ideale risicoprofiel voor het radiocurabele T1/T2 sinus pyriformis carcinoom is volume < 6,5 cm^3 en geen, of minimale uitbreiding naar de apex (lokale controle in deze studie 94%).

Hoofdstuk 5 beschrijft de rol van pre-RT CT bij het voorspellen van de kans op lokale tumorcontrole bij 63 patiënten met een bestraald supraglottisch larynx carcinoom. Het voorkomen werd geregistreerd van een lokaal recidief en complicaties tengevolge van RT, die een permanent verlies van de larynxfunctie tot gevolg hadden. Tumorvolume werd berekend met de 'summation-of-areas' techniek. Tumoruitbreiding in de pre-epiglottische ruimte werd gekwantificeerd. De lokale controle voor alle patiënten in deze studie bedroeg 70%. Tumorvolume was significant gerelateerd aan lokale controle. Voor tumoren < 6 cm^3 werd lokale controle bereikt in 89% van de patiënten, terwijl voor tumoren ≥ 6 cm^3 de lokale controle 52% was. Het behoud van de larynxfunctie was ook significant gerelateerd aan tumorvolume: < 6 cm^3 (89%) vergeleken met ≥ 6 cm^3 (40%). Meer dan 25% tumoruitbreiding in de pre-epiglottische ruimte was geassocieerd met een verminderde kans op het behoud van de larynxfunctie. De conclusie van dit onderzoek was dat met pre-RT CT volumemetingen patiënten met een bestraald supraglottisch larynx carcinoom ingedeeld kunnen worden in groepen waarin het bereiken van lokale controle na RT meer en minder waarschijnlijk is. Tumoruitbreiding in de pre-epiglottische ruimte is geen contra-indicatie voor RT als primaire behandeling van supraglottisch larynx carcinoom.

Hoofdstuk 6 betreft een onderzoek naar de rol van pre- en post-RT CT bij het voorspellen van de kans op lokale controle bij patiënten met een bestraald larynx carcinoom. Pre- and post-RT CT scans van 59 patiënten (T3 glottisch carcinoom; n = 30 en T1 - T4 supraglottisch carcinoom; n = 29) werden beoordeeld. Lokale controle werd gedefinieerd als de afwezigheid van een lokaal recidief en een functionerende larynx. Op basis van de pre-RT CT werd aan iedere primaire tumor een hoog of laag risicoprofiel voor het ontwikkelen van een lokaal recidief na bestraling toegekend. De post-RT CT scans werden met een drie-punts post-RT CT score beoordeeld op veranderingen tengevolge van de bestraling: Daarbij staat score 1 voor normale veranderingen na bestraling; score 2 voor focale massa met een maximale diameter van < 1cm en/of asymmetrische obliteratie van de endolaryngeale weke delen en score 3 voor focale massa met een maximale diameter van > 1cm, of < 50% geschatte afname van tumorvolume. De interpretatie van de verschillende post-RT CT-scores was: 1 = lokale controle zeer waarschijnlijk;

2 = onzeker; 3 = verdacht voor lokaal recidief. De lokale controle twee jaar na bestraling, gebaseerd op evaluatie van de pre-RT CT scan bedroeg 88% voor patiënten met een laag pre-RT risicoprofiel en 34% voor patiënten met een hoog pre-RT risicoprofiel. Gebaseerd op evaluatie van post-RT CT scans was de lokale controle twee jaar na bestraling: 94% voor score 1, 67% voor score 2 en 10% voor score 3. Bij combinatie van het post-RT CT-scoringssysteem met de twee pre-RT risicogroepen ontstond in beide groepen een verdeling in drie patiëntencategoriën met een toenemend risico op het krijgen van een lokaal recidief. Hierdoor was het mogelijk om patiënten te detecteren die een laag pre-RT risicoprofiel hadden en ongunstig reageerden op bestraling. Ook werden patiënten geïdentificeerd die een hoog pre-RT risicoprofiel hadden en gunstig reageerden op bestraling. De post-RT CT-score had een betere voorspellende waarde dan het pre-RT risicoprofiel. Geconcludeerd wordt dat zowel met pre-RT CT-risicoprofielen als met post-RT CT-evaluatie patiënten geïdentificeerd kunnen worden die na bestraling voor larynx-carcinoom een hoog risico hebben op het ontwikkelen van een lokaal recidief.

In *Hoofdstuk 7* worden de onderzoeksresultaten uit dit proefschrift besproken, toekomstige ontwikkelingen geschetst, en suggesties gedaan voor verder onderzoek.

Nawoord

Onderzoek doen en een proefschrift schrijven is een kwestie van engelengeduld. Veel gaat zoals gewenst, veel ook niet. Steeds waren er mensen die mij weer inspireerden, nieuwe invalshoeken lieten zien en andere mogelijkheden toonden. Mede-auteurs, reviewers en technici hebben hun bijdrage geleverd aan het tot stand komen van dit proefschrift. Collega's, medewerkers, vrienden, kinderoppassen en familieleden zorgden voor het in stand houden van de promovendus. Dankbaar ben ik voor alle hulp en loyale steun die ik van u ontvangen heb.

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Curriculum Vitae

Frank Alexander Pameijer was born on February 25, 1961 in Willemstad (Dutch Antilles).

In 1978 he graduated from the Gemeentelijk Gymnasium (City High School) in Hilversum. In the same year, he started his medical studies at Utrecht University, and obtained his medical degree in 1987.

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From 1989 to 1995 he was a resident in diagnostic radiology at Utrecht University Hospital (Prof. Dr. P.F.G.M. van Waes). During his training he became interested in volumetry using Computed Tomography. In the last year of his residency he participated in the Armed Forces Pathology Course, Armed Forces Institute of Pathology, Washington D.C., USA.

In 1995 he received a two-year clinical fellowship sponsored by the Dutch Cancer Society. As fellow, he worked at the Departments of Radiology at various institutions: The Netherlands Cancer Institute / Antoni van Leeuwenhoek Hospital, Amsterdam; the University of Florida, College of Medicine, Gainesville, USA; the Vrije Universiteit Hospital, Amsterdam, and the Academic Hospital Rotterdam Dijkzigt.

The research which culminated in this thesis was performed from 1995 to 1999. As from July 1997, the author has been working as a radiologist at the Netherlands Cancer Institute / Antoni van Leeuwenhoek Hospital.

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