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Laryngectomy Whole Organ Serial Sections

Histological Parameters Correlated with Recurrence Rate

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Whole organ sections of laryngectomy specimens, collected over a 10-year period (1976–1985) from 118 patients with carcinoma of the larynx, were reviewed. The aim of the investigation was to compare the histopathological data with the rate of recurrence to evaluate which factors were most significant in predicting recurrence. Epitome χ^2 analysis of frequency tables using corrected Yates' values revealed significant association between the recurrence rate and the depth of tumor infiltration, the presence of tumor cells at the surgical margins and the pathological TNM (tumor, nodes, metastases) stage. Multiple regression analysis identified perineural and thyroid gland tumor infiltration, anatomical location of the primary tumor and depth of tumor infiltration as independent predictors of recurrence. The greater the number of poor prognostic factors, the higher the risk for recurrence. Exact histopathological investigations integrated with clinical examinations and close patient follow-up are important and should be supported by statistical analysis to give a prognostic basis for the selection and evaluation of the treatment.

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Improved methods of total, whole organ sectioning have reduced the time for preparation of the slides for microscopic examination (1–4). By using rapidly acting decalcification and fixative solutions, the overall time for completing the procedure has been reduced to approximately 5 days. Good preservation of histological structures has been the main advantage. More selective serial sectioning of the specimens has adequately delineated the extent of the tumor (4).

The Association of Directors of Anatomic and Surgical Pathology have issued recommendations for the reporting of specimens containing laryngeal neoplasms (5). The purpose has been to provide an informative report for the clinician with the intention of offering an educational resource. The report should contain a description of the depth of tumor invasion with respect to anatomical landmarks such as specific cartilages and extralaryngeal structures. The tracheostomy site, if present, should be examined for tumor cells. Included in the report should also be the histological type, grade and extent of tumor, and comments on whether or not neural, vascular, pre-epiglottic or paraglottic space invasion is present. Comments on keratin debris and preoperative treatment effects on histopathology of lymph nodes should be included. Several tumor features are optional, such as tumor interface with stroma (superficial or deep infiltration, and nature of tumor boundary), distance of tumor border from surgical margins, type or density of inflammatory stromal infiltrate, and extent of any dysplasia (e.g. carcinoma in situ). These recommendations served as a background for our studies.

The practice of random sampling of the operative specimen for histological examination seems inadequate because it often fails to assess the entire extent of the tumor. Important prognostic information might therefore be lost. Statistical methods can correlate histopathological data with the recurrence rate and help to evaluate which factors are most significant.

Primary surgery, radiotherapy with surgery in reserve, planned preoperative or postoperative radiotherapy combined with conservation partial laryngectomy or radical surgery are discussed as optimal treatments for different stages of laryngeal squamous cell carcinoma. The working hypothesis for our study is that whole organ serial sections can contribute significantly to selection of optimal therapy and to prediction of subsequent recurrence.

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MATERIAL AND METHODS

The material consists of 118 consecutive laryngectomy specimens collected from 1976 to 1985. The clinical data of the patients are summarized in Table 1. Six patients with unknown outcome were excluded from the statistical evaluation. Thirteen patients without reports on the presence or absence of tumor cells at the surgical margins were also excluded when this variable was investigated. We observed that including patients with unknown outcome or no reports will sometimes result in spurious statistical figures.

A preponderance of elderly males with advanced squamous cell carcinoma is evident. The median age is 63 years

Table 1

Description of patient material (figures in parentheses represent percentages)

	Number	Recurrence	Pearson χ^2 analysis p-value	Yates' corrected χ^2 Statcalc analysis p-value
Males	104	44 (42)	0.95	0.44
Females	14	4 (29)		
Age (years)			0.90	40–59 vs. > 60
40–49	4	1		0.92
50–59	37	16 (43)		
60–69	53	23 (43)		
≥ 70	24	8 (33)		
Total	118	48 (41)		
Location			0.16	Supraglottic vs. glottic
Supraglottic	52	25 (48)		0.0334
Glottic	41	11 (27)		
Subglottic	2	0		
Transglottic	17	9 (53)		
Hypopharynx	6	3		
Clinical stage			0.0015	T1N0–T4N0 vs. T2N1–T4N3
T1N0	13	3 (23)		0.0013
T2N0	20	5 (25)		
T3N0	25	7 (28)		
T4N0	28	10 (36)		
T2–T4N1	22	15 (68)		
T3–T4N2N3	10	8 (80)		
Lymph node metastases			< 0.0001	0.0024
Yes	21	20 (95)		
No	97	28 (29)		
Plan of radiation and surgical therapy			0.57	Pre-/postoperative vs. salvage
Preoperative	49	24 (49)		0.33
Postoperative	24	10 (42)		
Salvage surgery	43	13 (30)		
Surgery alone	2	1		
Type of radiation			0.19	Megavoltage vs. kilovoltage
Megavoltage	65	26 (40)		0.92
Kilovoltage	51	21 (41)		
None	2	1		
Dose of radiation			0.0937	< 50 Gy vs. > 51 Gy
Megavoltage				0.75
≤ 50 Gy	21	10 (48)		< 5000 R vs. > 5001 R
51–66 Gy	21	7 (33)		0.12
67–70 Gy	23	9 (39)		
Kilovoltage	21	4 (19)		
< 5000 R	30	17 (57)		
> 5001 R	2	1		
None 1				
Type of surgery			< 0.0001	Laryngectomy alone vs. other
Laryngectomy alone	80	23 (29)		0.001
+ Radical neck dissection	18	14 (78)		
+ Partial pharyngectomy	4	1		
+ Preliminary tracheostomy	9	4		
+ Partial pharyngectomy and radical neck dissection	5	4		
+ Partial tongue resection	2	2		

(range 41–78 years). No significant change in age or sex distribution occurred over this period, and the pathological stage of the tumors was also similar except that a slight preponderance of advanced stages with lymph node metastases was observed during the last part of the decade. This difference was of borderline significance ($p = 0.0458$).

Most primary tumors were located in the supraglottic region with the glottic region second. Transglottic tumors were next in frequency. Six tumors proved, on subsequent detailed analysis, to be primary hypopharyngeal tumors with secondary invasion of the larynx. The clinical stage was described as advanced in 85 cases and 32 of these had palpable neck nodes.

The plan of the therapy consisted of preoperative irradiation followed by surgery in 49 cases and primary surgery followed by postoperative irradiation in 24; salvage surgery after a full dose of primary irradiation was required in 43 cases because of persistent tumor or complications. Surgery alone was performed in only two patients. No changes in the principles of treatment planning or execution were observed. Initially, kilovoltage irradiation with 200 kV was used in 51 cases. In 1978, megavoltage ($cobalt^{60}$) became available. The dose with megavoltage radiation was expressed in grays (Gy) to the tumor area whereas with kilovoltage radiation the roentgen (R) was the unit used. Opposing lateral fields were used routinely. The operation consisted of total laryngectomy in most cases but was supplemented with radical neck dissection and partial pharyngectomy or glossectomy in a few patients. Preliminary emergency tracheostomy due to airway obstruction was performed in nine cases.

The resected larynx was opened in the posterior midline and the gross appearance with the extension of the tumor was described. Supplementary drawings and color photographs were obtained in a number of cases. The entire laryngeal specimen was subjected to fixation in 10% formalin–saline for a minimum of 3 days and decalcified in 30% formic acid/citric acid mixture for 7–10 days depending on the degree of cartilage calcification. Multiple vertical, coronal or sagittal serial sections, approximately 3 mm thick, were cut with the microtome at right angles to the mucosa. The sections were stained with hematoxylin–eosin and subjected to detailed microscopic scrutiny. The subepithelial depth of tumor was measured on the slide with an ocular micrometer. The pathologist had no prior knowledge of the initial clinical diagnosis or the postoperative course of the patients.

Increased numbers and morphological changes of the fibroblasts expressed by variations in the nuclei, some with irregular, star-formed borders, hyperchromatism and abnormal proliferation, were termed pseudosarcomatous stromal changes. They were considered to be secondary to previous therapy.

The clinical data were extracted from the hospital records and supplemented with follow-up information provided by the Cancer Registry of Norway or by the referring physicians, local hospitals or near relatives. All data were analyzed using the BMDP statistical package (6). The variables were analyzed by frequency cross-tabulation to evaluate the relationship of the different variables to the recurrence rate. The Pearson χ^2-test was used to evaluate the significance of the differences. Because of expected small cell values in the table, we grouped the outcome as no recurrence, local and/or regional recurrence, and distant metastases, or grouped them as recurrence absent and recurrence present. In addition, while the data are presented in the tables in disaggregated form, we merged some predictor variables, excluding unreported variables and patients whose outcome was unknown, in order to adhere to the statistical assumptions of the χ^2 and to optimize univariate and multiple regression analyses. The Yates' corrected test was used for the two-by-two tables derived. All p-values reported are obtained from Statcalc, Yates' corrected χ^2, two-tailed Fisher's exact or Mantel–Haenszel calculations. To estimate the influence of confounding variables, stepwise, multiple regression equations were used to determine adjusted estimates of variables that influenced the recurrence rate. The p-value expressed the probability of significance of independent influence of the variables.

Small numbers of patients in specific cells of tables made standard Pearson χ^2 probability calculations inappropriate without Yates' correction for small numbers. Grouping of several cells with similar contents increased the power of the statistics.

RESULTS

The change from kilovoltage to megavoltage radiation did not cause any significant difference in the recurrence rate (Table 1). Among the clinical variables, the presence of lymph node metastases, TNM (tumor, nodes, metastases) staging, primary tumor location and type of surgery were significantly associated with recurrence rate on univariate analysis ($p < 0.05$) (Table 1). The recurrence rate increased with advancing clinical stage and extent of surgery. Multiple regression analysis confirmed lymph node metastases and TNM staging as independent variables, whereas type of operation did not quite reach significant probability, and primary tumor location had no independent influence on recurrence rate (Table 2).

Preliminary emergency tracheostomy seemed to have an unfavorable association with prognosis as four of nine patients developed recurrence, but it was not a statistically significant independent variable being confounded by other variables such as clinical stage, type of operation, depth of tumor infiltration and extension. Other clinical variables such as patient sex and age, plan of therapy (pre- or

Table 2

Tumor recurrence: multiple linear regression analysis of clinical and histopathologic parameters (patients with no reports or unknown outcome excluded)

	p-value
Clinical	
Lymph node metastases	< 0.0001
TNM staging	0.0043
Type of operation	0.0761
Plan of therapy	0.2558
Tumor location	0.7808
Pathological	
Perineural tumor infiltration	0.0076
Anatomical tumor location	0.0196
Tumor invasion of thyroid gland	0.0203
Depth of tumor infiltration	0.0483
Cartilaginous necrosis	0.0574
Pathological TNM staging	0.0706
Tumor infiltration of cartilage	0.1181
Surgical margins	0.1246
Vascular infiltration	0.2113
Tumor differentiation	0.3010
Pseudosarcomatous stroma	0.5892
Muscle infiltration	0.6193
Tumor necrosis	0.6947

postoperative irradiation or salvage surgery), type and dose of radiation, and gross appearance of the tumor did not reach significance on statistical analysis.

The following histopathological variables were found to be significant in univariate or multivariate analysis ($p < 0.05$).

Perineural tumor infiltration

In four specimens, perineural tumor infiltration of small nerve fibers and invasion of the cartilage was identified, and all four patients developed recurrence. Multiple regression analysis suggested probable independent significant association between perineural tumor infiltration and recurrence rate ($p = 0.0076$) (Table 2).

Tumor infiltration of the thyroid gland

In three specimens, tumor infiltration of the thyroid gland was identified, and none of these patients remained free of recurrence. Cartilaginous, perineural and vascular tumor infiltration was noted in all three specimens. Transglottic involvement was present in two. Multiple regression analysis suggested probable significant association with recurrence rate ($p = 0.0203$) (Table 2).

Primary tumor location (Table 3)

Although clinical determination of primary tumor location had suggested no significant association with the location of the primary tumor and recurrence rate, pathological examination suggested possible significant correlation. The tumor control rate was 56% for patients with primary supraglottic compared with 73% for glottic tumors and only two of 11 transglottic tumors. The univariate analysis suggested that primary tumor location was significantly associated with recurrence rate (Pearson χ^2, $p = 0.0057$). Merged groups of supraglottic, transglottic and subglottic tumors compared with the group of glottic tumors revealed borderline significance of probability of association with recurrence rate (Yates' corrected χ^2, $p = 0.0672$; Mantel–Haenszel, $p = 0.0408$). Multivariate analysis suggested that primary tumor location was independently associated with recurrence rate ($p = 0.0196$).

Depth of tumor infiltration (Table 4)

The depth of tumor infiltration into the stroma at the primary tumor sites showed a strong correlation with the subsequent recurrence rate. In the group of patients with tumor extending 5 mm or less in depth, 73% remained recurrence-free, compared with 54% in the group with tumors that infiltrated more than 5 to 9 mm. When the depth of tumor infiltration extended to between 10 and 15 mm in depth, only 36% of the patients remained free of recurrence. All patients with tumor infiltration beyond 20 mm experienced recurrence. By merging variables into two groups separating superficial tumors (depth 5 mm or less) from more deeply infiltrating tumors (depth > 5mm), highly significant differences in recurrence rate were noted (75% vs. 49%) (Yates' corrected χ^2, $p = 0.0072$). Multivariate analysis suggested probable independent significance ($p = 0.0435$).

Tumor infiltration of surgical margins (Table 5)

The presence of tumor cells at the surgical margins of the laryngectomy specimens correlated significantly with the recurrence rate. When histopathological examination of the specimens revealed that the surgical resection margins were tumor free, 66% of the patients remained free of recurrence compared with only 8% when carcinoma was identified at the margins. In a few specimens, the tumor cells infiltrated close to the margins, and 56% of these patients had no recurrence. Groups of patients with positive margins and merged groups with negative, close or uncertain margins showed marked difference in recurrence rate with high probability of statistical significance on univariate analysis (Yates' corrected χ^2, $p = 0.0002$; Fisher's exact two-tailed, $p = 0.0001$). Multivariate analysis failed to confirm this as an independent variable ($p = 0.1246$).

Pathological TNM staging (Table 6)

Whereas 58–74% of patients without nodal metastases achieved tumor control, only one of 16 patients with metastatic lymph nodes in the neck survived without recurrence. Comparison of merged groups of patients without nodal metastases with merged groups with histo-

Table 3

Recurrence rate: influence of primary tumor anatomical location (figures in parentheses represent percentages) Pearson χ^2: p = 0.0057

Recurrence	Supraglottic	Glottic	Subglottic	Transglottic	Hypopharynx	Neck only	No tumor	Total
None	14 (56)	33 (73)	6	2	0	0	15	70
Local	4	2	1	1	0	0	1	9
Regional	3	4	1	1	0	1	3	13
Distant	1	2	0	2	1	0	4	10
Local+regional	0	1	0	1	0	0	2	4
Local+regional+distant	0	1	0	1	0	0	0	2
Regional+distant	0	1	0	3	0	0	0	4
Unknown	3	1	0	0	1	0	1	6
Total	25	45	8	11	2	1	26	118

Statcalc analysis (26 patients with negative laryngeal specimen or two with primary tumor originating in hypopharynx and 6 with unknown outcome are excluded)

Recurrence	Glottic	Supraglottic, transglottic or subglottic	Total
No	33 (75)	22 (54)	55
Yes	11	19	30
Total	44	41	85

Yates corrected χ^2: p = 0.0672.
Mantel–Haenszel: p = 0.0408.

Table 4

Recurrence rate: influence of depth of tumor infiltration by histopathologic examination (figures in parentheses represent percentages)

Recurrence	Depth of infiltration				Total
	0–5 mm	5.1–9 mm	10–14 mm	>15mm	
None	43 (73)	15 (54)	8 (36)	4 (57)	70
Local	2	1	5	1	9
Regional	5	5	3	0	13
Distant	4	1	3	2	10
Local+regional	3	1	0	0	4
Local+regional+distant	0	1	0	1	2
Regional+distant	0	1	2	1	4
Unknown	2	3	1	0	6
Total	59	28	22	9	118

Statcalc analysis (6 patients with unknown outcome excluded)

Recurrence	Depth of tumor infiltration		Total
	≤5 mm	>5.1 mm	
No	43 (75)	27 (49)	70
Yes	14	28	42
Total	57	55	112

Yates' corrected χ^2: p = 0.0072.

pathologically verified nodal metastases yielded a highly significant difference in recurrence rate (Yates' corrected χ^2, $p < 0.0001$). Multiple regression analysis suggested near significant probability of pathological TNM staging as an independent variable (p = 0.0706).

Stomal/peristomal recurrence

Five patients in the present series developed stomal/peristomal recurrence. They all died of recurrent tumor, three in the neck, one in the neck with distant metastases and one with local recurrence.

Table 5

Recurrence rate; influence of tumor infiltration of surgical margins (figures in parentheses represent percentages)

Recurrence	Surgical margins negative	Surgical margins positive	Surgical margins close	Surgical margins uncertain	No report	Total
None	53 (66)	1 (8)	5 (56)	2 (50)	9 (69)	70 (59)
Local	5	2	1	1	0	9 (8)
Regional	6	4	2	0	1	13 (11)
Distant	8	1	0	1	0	10 (8)
Local+regional	2	1	0	0	1	4
Local+regional+distant	0	2	0	0	0	2
Regional+distant	2	1	0	0	1	4
Unknown	4	0	1	0	1	6
Total	80 (100)	12 (100)	9 (100)	4 (100)	13 (100)	118 (100)

Statcalc analysis (13 patients with no report and 6 with unknown outcome excluded)

Recurrence	Surgical margins negative, close or uncertain	Surgical margins positive	Total
No	60 (68)	1 (8)	61
Yes	28	11	39
Total	88	12	100

Yates' corrected χ^2: $p = 0.0002$.
Fisher's exact test, two-tailed: $p = 0.0001$.

Table 6

Recurrence rate: influence of pathological tumor stage (figures in parentheses represent percentages)

Recurrence	T1N0	T2N0	T3N0	T4N0	N1	N3	T0N+	T0N0	Total
None	3	5	25 (74)	21 (68)	1	0	0	15 (58)	70
Local	0	0	2	5	1	0	0	1	9
Regional	0	0	2	2	1	4	1	3	13
Distant	0	1	1	1	1	2	0	4	10
Local+regional	0	0	2	0	0	0	0	2	4
Local+regional+distant	0	0	0	0	0	2	0	0	2
Regional+distant	0	0	1	1	1	1	0	0	4
Unknown	1	1	1	1	0	1	0	1	6
Total	4	7	34	31	5	10	1	26	118

Statcalc analysis (6 patients with unknown outcome excluded)

Recurrence	T0N0	T1–4N0	N1–N3	Total
No	15 (60)	54 (75)	1 (7)	70
Yes	10	18	14	42
Total	25	72	15	112

Yates corrected χ^2: $p < 0.0001$.

On multiple regression analysis, primary tumor location, clinical or pathological TNM staging, depth of tumor infiltration and perineural or thyroid gland tumor invasion were significantly associated with recurrence (Table 2).

Cartilaginous necrosis and tumor infiltration were of borderline significance. Some variables with significant probability of correlation with recurrence on univariate analysis were significantly associated with other variables. Multiple regression analysis tended to rule these out as independent variables influencing recurrence rate.

Among the variables that did not reach statistically significant association with recurrence were: tumor differentiation based on degree of keratinization, pleomorphism and mitotic rate, and tumor bed reactions. In 10 specimens extensive pseudosarcomatous stromal changes were reported and only three of these patients were free of recurrence, compared with 63% of those with less extensive or no similar stromal changes, but the difference was not of independent statistical significance. This was also the case with a number of other histopathological variables that were

overshadowed by many confounding factors such as tumor location and extension, depth of infiltration and lymph node metastases.

Distant metastases

Sixteen patients were diagnosed with distant metastases before death, too few for a meaningful multiple regression analysis. Distant metastases occurred most frequently among patients with extensive, deeply infiltrating, advanced tumors with metastases to lymph nodes in the neck.

DISCUSSION

Our present studies have served to call attention to certain histopathological findings that may be important for prediction of tumor recurrence.

Perineural tumor invasion

In our present series, perineural infiltration of a small nerve fiber was identified microscopically in four specimens and all these patients developed recurrence. Multiple regression analysis suggested perineural tumor infiltration as an independent variable. Perineural tumor invasion has been reported to be associated with increased incidence of nodal metastases (7, 8).

In a prospective, randomized trial including different head and neck cancers, nerve invasion was listed as a factor of increased risk of local–regional recurrence but only when associated with one or more additional adverse prognostic factors (9).

Tumor infiltration of the thyroid gland

In our series, thyroid gland involvement was demonstrated in three cases that all recurred despite radical surgery with thyroidectomy and irradiation. Thyroid gland involvement from carcinoma of the larynx has occurred chiefly among patients with extensive laryngeal involvement and subglottic extension. The lymph vessels from the subglottis drain into the paratracheal nodal chain on both sides. Direct invasion has been most frequent, but metastases to the thyroid gland can also occur. Eighteen of 23 patients died within 3 years, 15 due to stomal recurrence (10). An incidence of 2% thyroid gland involvement associated with carcinoma of the larynx has been reported, but additional patients have tumors extending to within millimeters of the thyroid gland capsule (11).

Depth of tumor infiltration

The present study showed that the depth of tumor infiltration as measured on the microscopic slide was a significant independent variable associated with recurrence rate. The depth of tumor infiltration has also been significantly correlated with the incidence of lymph node metastases (7).

Earlier studies have described the pathological extent of tumors perpendicular to the mucosa in the terms of pathological (P) stage (12). The P-stage correlated more closely with the clinical course and the survival of the patients than with the conventional T-stage as defined at that time. A true appreciation of deep soft tissue extent of the primary carcinoma was necessary for a more precise evaluation of a given tumor.

The negative correlation between the depth of tumor invasion and the patients' disease-free survival has been shown to be statistically significant in a group of surgically treated patients with T1–T3 laryngeal cancers: the deeper the tumor invasion, the shorter the disease-free survival. Patients with no clinical involvement of the regional lymph nodes (N0) had significantly less depth of tumor invasion than had those with nodal involvement (N+) (13).

Computerized axial tomography and magnetic resonance imaging have made it possible to estimate depth of tumor infiltration clinically before the operation (14).

Tumor infiltration of surgical margins

Our studies confirmed that positive surgical margins lower the recurrence-free rate but any independent statistical significance on multivariate analysis could not be detected.

Other studies have given convincing evidence for the prognostic significance of positive surgical margins (15–19). Multivariate analysis has identified positive resection margins as a significant independent variable that influences the corrected actuarial survival of patients with laryngeal carcinoma with or without lymph node metastases (18, 19).

Tumor invasion of the surgical margins after conservation surgery for radiation failure of glottic carcinoma has been independently associated with survival and was the only risk factor for local recurrence (20).

Delineation of the surgical margins is not always accurate because of limitations inherent in the examination of surgical specimens. Differential retraction and curling of the tissues at the margins can distort normal tissue relationships, thus exposing tumor cells at a surface that is not really a surgical margin. Such difficulties can explain the lack of correlation observed by some authors between recurrence rate and the tumor involvement of surgical margins (17).

Accurate delineation of the extent of the primary lesion is not always possible on clinical examination. It is particularly difficult to assess the extent of the local tumor after irradiation has failed to control the local carcinoma. Often the bulk of the tumor has shrunk, but islands of carcinoma cells may remain within the original extent of the tumor (18). In many cases, scattered tumor cells can be seen to follow vessels and mucous glandular ducts into distant sites within the larynx. Therefore, sections of the tumor margins may not define the extent of the tumor at the time of surgery (19).

Tumor infiltration of laryngeal muscles

Our studies did not succeed in demonstrating that tumor infiltration of the laryngeal muscle tissue was associated with increased recurrence rate despite evidence from other studies that fixation of the vocal is an ominous finding (20).

Previous histopathological studies of serial sections have demonstrated tumor invasion of the thyroarytenoid muscle of patients who have had fixation of the vocal cord (21, 22). Impaired cord mobility has been an increased independent risk for recurrence (23).

Vocal cord mobility has been the best discriminating factor between local control and failure in the early stages of glottic cancer as demonstrated on multivariate analysis (24). Radiation fibrosis without residual tumor can cause fixation of the vocal cord (25). The fibrosis can presumably involve the crico-arytenoid joint. However, radiation fibrosis as the sole cause of fixation has not been observed in serial sections (26). With increasing degree of cord fixation, the local recurrence rate has increased (27).

Stomal/peristomal recurrence

Our present studies confirmed stomal/peristomal recurrence as a fatal event. Stomal/peristomal recurrence may develop as a painless, diffuse infiltrate of neoplastic tissue or may look like exuberant granulations at the junction of the amputated trachea and the skin. It may be localized to one side or encircle the stoma (28). Tumor recurrence may develop adjacent to the stoma and grow from the mucocutaneous junction of the tracheostomy or the scar in the skin. Stomal recurrence has usually been associated with extensive tumors that extend into the submucosa of the subglottis and often erode through cartilage into the extralaryngeal tissues (29, 30).

The only cures of stomal recurrence have been achieved for patients with small nodular recurrences in the superior part of the stoma (31). Subglottic and postcricoid involvement are independent risk factors for tracheostomal recurrence. Preoperative airway obstruction is considered a significant factor (30).

Tumor infiltration of the vascular structures

In our present series, an association between vascular invasion and recurrence rate could not be demonstrated. Neither could we demonstrate significant correlation between vascular tumor invasion and tumor grade or lymph node metastases. Penetration of the vascular channels by tumor cells has been believed to be a reliable indicator of the tumor's aggressive character (32); many pathologists interpret carcinoma cells in vascular spaces as precursors to metastases (33). By histochemical methods it has been found that tumor vascular invasion independently predicts cervical node metastases in laryngeal carcinoma (34). The microvascular density of laryngeal carcinomatous tissue, as determined by immunohistochemical methods, seems to be higher than in normal laryngeal tissues (35). There is reason to believe that not all cancer cells within vascular spaces will develop into metastases (36, 37). Invasion of small venous channels in cases of laryngeal squamous cell carcinoma has not been associated with an increase in incidence of lymph node metastases in other studies (33).

A significant correlation between low vascular density and increased risk of recurrence has been observed in a group of patients with T1T2N0 squamous cell carcinoma of the vocal cord, treated with irradiation. The blood vessels were visualized by an immunohistochemical method and vessel density was measured with good intra- and inter-observer reproducibility. Vascular density was a significant prognostic factor on multivariate analysis. Cancers with high vessel density responded well to irradiation, whereas cancers with low vessel density showed increased risk of recurrence (38).

The vascularity of the tumor bed is important in ascertaining a good radiotherapeutic effect on the carcinoma cells. The radiation response from the vasculo-connective tissues influences the radiation sensitivity of the carcinoma cells. Inappropriately high daily radiation doses result in fibrosclerosis with reduced oxygenation and nourishment of the tissues with adverse effect on the radiosensitivity of the tumor cells (39).

Tumor necrosis

In our present study, extensive tumor necrosis showed no association with recurrence. Other investigators have found that necrotic tumors have been associated with increased incidence of lymph node metastases (27). Large tumors are often ulcerated, edematous with fixation or markedly reduced mobility. Although extensive tumor or tissue necrosis might be expected to increase the spread of carcinoma cells by facilitating their entrance into the microcirculation, we found no evidence of increased frequency of distant metastases in our material of necrotic tumors.

Tumor bed reactions

In our series, pronounced pseudosarcomatous was associated with high recurrence rate, but significant probability of independent statistical correlation could not be demonstrated. Lymphocyte/plasma cell infiltration at the tumor–host tissue interface was not associated with decreased tumor recurrence rate.

Infiltration of Langerhans cells among the cancer cells had no significant relationship with recurrence rate. Other investigators have suggested that peritumoral infiltration with a great number of Langerhans and plasma cells has a favorable influence on the survival of patients with laryngeal carcinoma after radiation and surgical treatment (40–42).

While the tumor bed plays a significant role in tumor development and response to therapy, the exact mechanism of the interaction between tumor cells and the surrounding stroma remains obscure.

Comments

The methods of whole organ, serial sectioning of laryngectomy specimens can provide significant information and aid in predicting subsequent probability of recurrence of patients operated for cancer of the larynx. Special attention should be paid to depth of tumor infiltration, perineural tumor infiltration, and infiltration of the thyroid gland as well as other extralaryngeal tissues. The presence of tumor cells at the surgical margins is confounded by other variables.

A detailed pathological report based on serial sections is of great help to the clinician in predicting prognosis and future planning of patient management.

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