Role of Postoperative Radiotherapy in Nonmetastatic Head and Neck Adenoid Cystic Carcinoma

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ABSTRACT

Background: Head and neck adenoid cystic carcinoma (ACC) is a rare malignant tumor that is prone to local recurrence. The NCCN Guidelines for Head and Neck Cancers recommend that all patients with ACC receive postoperative radiotherapy (PORT). However, whether PORT can improve local control and which patients can benefit from PORT are unknown. This study aimed to assess the role of PORT and provide individualized suggestions for postoperative therapy in patients with ACC. **Patients and Methods:** We retrospectively reviewed patients with nonmetastatic head and neck ACC who underwent surgery with or without PORT. Recursive partitioning analysis (RPA) was performed to categorize the patients and predict local recurrence-free survival (LRFS). The survival outcome was compared between non-PORT and PORT groups. **Results:** A total of 319 patients were included. PORT was identified as a prognostic factor for LRFS in univariate ($P=.01$) and multivariate analysis ($P<.01$). However, it did not improve distant metastasis-free survival, disease-free survival, or overall survival in univariate analysis. RPA categorized patients into 3 prognostic groups: low-risk (negative margin, T1–T2, primary location = major or minor salivary gland), intermediate-risk (negative margin, T1–T2, primary location = other locations instead of a major or minor salivary gland; negative margin, T3–T4; positive margin, without bone invasion), and high-risk (positive margin, with bone invasion). Significant LRFS improvements in the PORT group were observed among intermediate-risk ($P<.01$) and high-risk patients ($P<.05$). LRFS improvements among low-risk patients were relatively insignificant ($P=.10$). **Conclusions:** PORT was shown to be a positive prognostic factor for improved LRFS in ACC. Furthermore, PORT could significantly improve LRFS in intermediate-risk and high-risk patients with ACC, but whether low-risk patients could benefit from PORT needs further study.

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Background

Adenoid cystic carcinoma (ACC) is a rare low-grade malignant tumor, accounting for approximately 1% of all head and neck malignancies.¹ ACC usually originates from many types of glands and most often arises in salivary glands, accounting for 25% of malignant tumors in the major salivary glands and 50% in the minor glands.² The natural disease process is characterized by prolonged progression and multiple recurrences.^{3,4}

Surgery has been considered the most important treatment of ACC.⁵ However, because of the unique anatomic structures of the head and neck, the scope of surgery is often limited. Moreover, ACC is prone to local nerve invasion, and therefore it is often difficult to remove the tumor completely. Consequently, postoperative radiotherapy (PORT) is often considered an important adjuvant treatment after surgery. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Head and Neck Cancers have a category 2B recommendation for patients with T1 ACC and a category 2A recommendation for other patients with ACC to receive additional PORT after complete resection.⁶ However, whether PORT can improve local control in patients with ACC remains controversial,^{3,5,7–9} and which patients need additional PORT often confuses surgeons and radiologists.

Given the rarity of ACC and the difficulty of conducting relevant prospective clinical trials, we conducted a retrospective study of a large sample of patients with nonmetastatic head and neck ACC to elucidate the role of PORT in survival outcome, which would help surgeons and radiologists provide individualized recommendations regarding PORT to patients with ACC.

Patients and Methods

Patient Characteristics

From January 2000 through December 2017, 480 patients were pathologically diagnosed with head and neck ACC and treated in Sun Yat-sen University Cancer Center in

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China. The following patients were excluded: 115 patients who received their initial surgery in other hospitals without accurate baseline data, 31 who did not receive surgery, 14 with initial distant metastasis, and 9 lost to follow-up within 3 months after treatment. Therefore, we focused on 319 patients who had undergone surgery with or without PORT after the first diagnosis. The characteristics of the 319 patients are shown in Table 1. Detailed primary sublocations of ACC are shown in supplemental eTable 1 (available with this article at JNCCN.org). In our study, 32 patients with nerve invasion did not receive PORT: 10 could not afford the cost of PORT; 8 due to elderly age; 7 failed to follow doctors' orders; 6 due to wound infection, poor healing, and weakness; and 1 worried about the adverse effects of radiotherapy (RT) and chose postoperative chemotherapy.

Treatment Methods

Surgery

Of the 319 patients included, 92 (28.8%) underwent surgery alone and the remaining 227 (71.2%) received PORT. As for the operative method, 232 (72.7%) underwent resection of the primary location alone, whereas 87 (27.3%) also received resection of cervical lymph nodes. Indications for neck dissection were as follows: clinically positive lymph nodes; large T tumors; patients whose neck would be perforated or open during operation; or patients who needed free cervical flaps for repair. The extent of lymph node dissection was at the surgeon's discretion, mainly based on the patients' medical histories, clinical palpation, imaging data, and intraoperative exploration. If there were several clinically positive lymph nodes, a large volume of lymph nodes, extranodal invasion, or T3–T4 tumors, unilateral cervical lymph node resection was performed. Otherwise, limited regional lymph node dissection was performed. Of the 87 patients who underwent neck dissection, 6 nodes per patient were dissected on average.

Radiotherapy

Indications for PORT included large primary tumor, nerve invasion, positive margins, or the surgeons considered the primary tumor unresectable and recommended PORT. Different RT techniques were used: 81 patients received 2D RT, 25 received 3D conformal RT (3D-CRT), and 213 received intensity-modulated RT (IMRT). For patients treated with 3D-CRT and IMRT, the gross tumor volume (GTV) of the RT target was delineated basing on preoperative and postoperative contrast-enhanced CT or contrast-enhanced MRI, including the region with positive margin and persistent enhancement after surgery. In patients with large T tumor invading deep tissues or the skull base that could

Table 1. Baseline Characteristics of Study Cohort

Characteristic	Total n (%)	Non-PORT n (%)	PORT n (%)	P Value
Total, N	319	92	227	
Age, y				.03
≤47	169 (53.0)	40 (43.5)	129 (56.8)	
>47	150 (47.0)	52 (56.5)	98 (43.2)	
Sex				.44
Male	139 (43.6)	37 (40.2)	102 (44.9)	
Female	180 (56.4)	55 (59.7)	125 (55.0)	
Alcohol history				.64
No	306 (95.9)	89 (96.7)	217 (95.6)	
Yes	13 (4.1)	3 (3.3)	10 (4.4)	
Tobacco history				.74
No	267 (83.7)	76 (82.6)	191 (84.1)	
Yes	52 (16.3)	16 (17.4)	36 (15.9)	
Primary tumor location				.14
Major salivary gland	97 (30.4)	35 (38.0)	62 (27.3)	
Minor salivary gland	189 (59.2)	47 (51.1)	142 (62.6)	
Other	33 (10.3)	10 (10.9)	23 (10.1)	
Nerve invasion				.82
No	211 (66.1)	60 (65.2)	151 (66.5)	
Yes	108 (33.9)	32 (34.8)	6 (2.6)	
Vessel invasion				.52
No	301 (94.4)	88 (95.7)	213 (93.8)	
Yes	18 (5.6)	4 (4.3)	14 (6.2)	
Bone invasion				<.01
No	242 (75.8)	81 (88.0)	161 (70.9)	
Yes	77 (24.1)	11 (12.0)	66 (29.1)	
Surgical margin				.01
Negative	239 (74.9)	78 (84.8)	161 (70.9)	
Positive	80 (25.1)	14 (15.2)	66 (29.1)	
T stage				<.01
T1–T2	146 (45.8)	55 (60.0)	91 (40.1)	
T3–T4	173 (54.2)	37 (40.0)	136 (59.9)	
Lymph node metastasis				.38
No	302 (94.7)	85 (92.4)	217 (95.6)	
Yes	17 (5.3)	7 (7.6)	10 (4.4)	
Concurrent chemotherapy				—
No	—	—	200 (88.1)	
Yes	—	—	27 (11.9)	

Abbreviation: PORT, postoperative radiotherapy.

hardly be completely removed by surgery, GTV included these sites. The clinical target volume (CTV) extended 5 to 10 mm beyond the GTV. If the tumor invaded the main nerves, the CTV included not only the postoperative primary bed but also the potential path of the

main nerves along with intracranial or peripheral invasion, examples of which are shown in supplemental eFigures 1 and 2. As for pathologically positive cervical lymph nodes, a certain cervical region was included in the CTV. The planning target volume (PTV) was a 5-mm extension of CTV. In 92% of cases, the planning target volume of the GTV and/or the involved lymph nodes was generally given as a total dose of 60 to 72 Gy. In patients with residual primary tumors or positive lymph nodes, the prescription dose was 66 to 72 Gy. For patients with adverse features but the tumor was completely resected, the dose was 60 to 66 Gy.

Patient Follow-Up and Statistical Analysis

After the first visit to our hospital, the patients were followed up every 3 months in the first 2 years, and every 6 months thereafter until the patients died. Local recurrence-free survival (LRFS) was defined as the time from the beginning of treatment to the first recurrence at the primary location.⁷ Patients with regional recurrence were not included. Distant metastasis-free survival (DMFS) was defined as the time from the beginning of

treatment to the first recurrence at a distant location. Pathologic confirmation or radiographic evidence (CT, MRI, or PET/CT) was necessary for the diagnosis of local recurrence or distant metastasis. Overall survival (OS) was defined as the time from the beginning of treatment to death or the last follow-up. Disease-free survival (DFS) was defined as the time from the beginning of treatment to tumor progression, death, or the last follow-up.

Patients were divided into 2 groups based on whether they received PORT or not: PORT and non-PORT. The clinicopathologic factors of these groups were compared using the chi-square test. Cumulative survival rates were estimated using the Kaplan-Meier method and compared with the log-rank tests. Multivariate Cox regression analysis was performed to confirm the role of PORT in LRFS when adjusted for other possible factors by using the enter algorithm. We included age, sex, alcohol history, tobacco history, primary tumor location, nerve invasion, vessel invasion, bone invasion, surgical margin, T stage, lymph node metastasis, and PORT in the Cox model. Moreover, forest plots were generated to summarize the adjusted hazard ratios (HRs)

Figure 1. Rates of (A) LRFS, (B) DMFS, (C) DFS, and (D) OS in patients with adenoid cystic carcinoma.

Abbreviations: DFS, disease-free survival; DMFS, distant metastasis-free survival; LRFS, local recurrence-free survival; OS, overall survival.

with 95% confidence intervals for the validated predictors of LRFS.

Recursive partitioning analysis (RPA) for LRFS was based on the same variables except for PORT. To ensure a sufficient number of patients were included in the analysis of subgroups, a viable split was considered when at least 50 patients were in each group and the *P* value was statistically significant, as described elsewhere.¹⁰ To attain the patients most likely to benefit from PORT, we performed individual comparisons of non-PORT and PORT for each risk group. Statistical analyses were performed using SPSS Statistics, version 24 (IBM Corp) or the RMS package in R version 3.5.2 (R Foundation for Statistical Computing). The forest plots were generated using Microsoft Excel (Microsoft Inc). All *P* values were 2-sided with significance defined as a *P* < .05.

Results

Survival Outcomes

After a median follow-up of 64 months (range, 5–227 months), 63 of 319 patients (20%) developed local recurrence, 64 (20%) developed distant metastasis, 133 (42%) experienced tumor progression or death, and 64 (20%) died. In our study, 29 people died within 5 years (25 died of a tumor, 2 of natural aging, 1 of cardiovascular and cerebrovascular diseases, and 1 because of an accident); 22 people died between 5 and 10 years (16 died of a tumor, 3 of cardiovascular and cerebrovascular diseases, 2 of natural aging, and 2 because of an accident).

Survival curves are shown in Figure 1. For the whole cohort, the 1-, 3-, 5-, and 10-year LRFS rates were 98%, 90%, 85%, and 66%, respectively; DMFS rates were 98%, 91%, 83%, and 69%, respectively; DFS rates were 98%, 80%, 67%, and 40%, respectively, and OS rates were 100%, 92%, 88%, and 71.1%, respectively.

Effect of PORT on LRFS

Patients in the PORT group were younger, with a greater proportion of bone invasion, positive surgical margins, and advanced T stage compared with the non-PORT group (Table 1). The 5-year LRFS, DMFS, DFS, and OS were 75%, 94%, 66%, and 90%, respectively, for the non-PORT group and 89%, 79%, 67%, and 88%, respectively, for the PORT group (Table 2).

In univariate analysis, PORT was a significant prognostic factor for LRFS (HR, 0.54; 95% CI, 0.33–0.89; *P* = .01) but not for DMFS (HR, 3.38; 95% CI, 1.65–6.95; *P* < .01), DFS (HR, 1.10; 95% CI, 0.76–1.60; *P* = .61), or OS (HR, 1.32; 95% CI, 0.76–2.30; *P* = .32) (Table 2). After adjusting for covariates, PORT remained an independent prognostic factor for LRFS (HR, 0.27; 95% CI, 0.15–0.48; *P* < .01) in multivariate analysis (Figure 2).

Table 2. Survival Outcome of Study Population

Outcome	Non-PORT (n=92)	PORT (n=227)	HR (95% CI)	P Value ^a
LRFS rate			0.54 (0.33–0.89)	.01
1-year	92%	98%		
3-year	86%	92%		
5-year	75%	89%		
10-year	61%	68%		
DMFS rate			3.38 (1.65–6.95)	<.01
1-year	100%	97%		
3-year	96%	89%		
5-year	94%	79%		
10-year	84%	63%		
DFS rate			1.10 (0.76–1.60)	.61
1-year	92%	97%		
3-year	82%	80%		
5-year	66%	67%		
10-year	45%	37%		
OS rate			1.32 (0.76–2.30)	.32
1-year	99%	99%		
3-year	93%	92%		
5-year	90%	88%		
10-year	71%	71%		

Abbreviations: DFS, disease-free survival; DMFS, distant metastasis-free survival; HR, hazard ratio; LRFS, local recurrence-free survival; OS, overall survival; PORT, postoperative radiotherapy.

^a*P* values were calculated by log-rank test.

RPA Model for LRFS

The RPA model was generated based on the endpoint of LRFS. The RPA algorithm segregated the 319 patients with ACC into 5 classes (Figure 3). Because the LRFS of classes 2, 3, and 4 were not significantly different (class 2 vs 3, *P* = .53; class 2 vs 4, *P* = .89; class 3 vs 4, *P* = .46), these 3 groups were combined. Therefore, the final RPA model categorized patients into the following 3 prognostic groups: low-risk (T1–T2 disease with negative margin, and primary location limited to the major or minor salivary gland; n = 112), intermediate-risk (T1–T2 disease with negative margin and the primary tumor located in other sites except salivary gland; T3–T4 disease with negative margin; or positive margin but without bone invasion; n = 167), and high-risk (positive margin with bone invasion; n = 40), with corresponding 5-year LRFS rates of 93%, 83%, and 44%, respectively (low-risk group: HR, 1.00; intermediate-risk group: HR, 3.12; 95% CI, 1.55–6.29; *P* < .01; high-risk group: HR, 7.60; 95% CI, 3.39–17.05; *P* < .01).

Role of PORT in the Risk Groups

The LRFS of the 3 risk groups categorized by RPA were significantly different from each other (all *P* < .017; Figure 4A). LRFS for each of the 3 groups is shown in

Figure 2. Forest plot analysis of local recurrence-free survival in patients with adenoid cystic carcinoma. Red *P* values are statistically significant. Abbreviations: HR, hazard ratio; PORT, postoperative radiotherapy.

Figure 4B, C, D, respectively. Compared with the non-PORT group, the patients receiving PORT had better LRFS in the intermediate-risk (HR, 0.39; 95% CI, 0.20–0.74; $P < .01$) and high-risk groups (HR, 0.34; 95% CI, 0.11–1.05; $P < .05$), whereas the difference was not significant in the low-risk group (HR, 0.34; 95% CI, 0.09–1.30; $P = .10$).

Other than LRFS, we also studied the role of PORT in DMFS. The *P* values for DMFS for the 3 risk groups were $< .01$, 0.23, and 0.28, respectively, and the patients with ACC failed to benefit from PORT in all 3 risk groups (supplemental eFigure 3).

Discussion

Although PORT has been used widely in clinical practice, it was unclear whether it could reduce the local

recurrence of ACC in patients, and which patients could benefit the most from this treatment. Our analysis showed that PORT can improve LRFS in patients with ACC; however, the benefit was more obvious in intermediate- and high-risk patients. Whether low-risk patients could benefit from PORT requires further study.

Local Failure in Patients With ACC

In our study, we found that the rate of LRFS, DMFS, DFS, and OS in patients with ACC had been decreasing continuously for 10 years after initial treatment. In contrast, tumor progression usually occurs within 5 years in other tumors, with the risk of recurrence or metastasis rates decreasing rapidly after 5 years.^{11–13} That is because ACC is a low-grade malignancy with slow growth.

Figure 3. Prognostic grouping by recursive partitioning analysis in patients with head and neck ACC for predicting LRFS.

Abbreviations: ACC, adenoid cystic carcinoma; HR, hazard ratio; LRFS, local recurrence-free survival.

^aPrimary tumor location limited to the major or minor salivary gland.

^bPrimary tumor located in sites other than the salivary glands.

Consistent with our findings, Jones et al¹⁴ found that the actuarial local recurrence rate was 83% at 20 years and increased to 100% at 30 years (n=104). The 5- and 10-year local control rates in a study by Chen et al¹⁵ were 88% and 77%, respectively (n=140). Iseli et al⁵ reported that the LRFS rate was 68.2% at 5 years and 40.8% at 10 years (n=183). We also found that the OS rate of ACC remained as high as 88% at 5 years and decreased rapidly to 71% at 10 years. A recent study by Ouyang et al¹⁶ that included >210 patients with ACC treated over 25 years reported 5- and 10-year OS rates of 85% and 71%, respectively, which were consistent with our data. These data suggest that ACC was characterized by an indolent but persistent course.

The mainstay treatment modality of ACC is surgery. Unfortunately, for ACC of the head and neck, the scope of surgery is largely limited by the complex and delicate anatomic structures. Typically, it is difficult to completely

remove the tumor and protect the organs at risk simultaneously. Radical surgery can result in probable disfigurement of the patient.^{2,5,17} To preserve patients' quality of life after surgery, surgeons often tend to minimize the scope of surgery, which can lead to a decline in the local recurrence rate.^{18,19}

Furthermore, our LRFS rate was 85% at 5 years and 66% at 10 years, which is similar to rates reported in previous studies.^{7,20} In our study, approximately 20% of patients eventually developed local recurrence, similar to the results of Zhang et al,²¹ whereas a study by Jang et al²² reported a local recurrence rate as high as 32%. Because ACC has been widely reported as a highly recurrent tumor in many other research studies,^{5,7,18,23} local recurrence is one of the main patterns of treatment failure in patients with ACC. Consequently, the key to improving the efficacy of treatment in patients with ACC is to reduce local recurrence.²⁴

Figure 4. Kaplan-Meier estimates of LRFS in different prognostic groups derived by recursive partitioning analysis. (A) LRFS in 3 prognostic groups. (B) PORT in the low-risk group. (C) PORT in the intermediate-risk group. (D) PORT in the high-risk group. Abbreviations: LRFS, local recurrence-free survival; PORT, postoperative radiotherapy.

Benefits of PORT

RT is one of the most important means of improving local control. It uses high-energy radiation to destroy the DNA of tumor cells via direct ionization or indirect ionization by photons or charged particles.^{25,26} The advantage of this technique over surgical treatment is that precise RT can protect normal tissues while killing tumors. A recent study of 87 patients with ACC over 20 years by Ali et al⁷ showed that patients who did not receive PORT had a 13-fold increased risk of local failure compared with those treated with PORT after adjusting for stage. Therefore, PORT may serve as an important adjuvant treatment for high-risk patients (especially those with residual tumor).^{27,28}

Our study showed that PORT could improve LRFS in patients with ACC but had no effect on DMFS, DFS, or OS, which is consistent with the findings of many other research studies.^{7,29,30} One reason for this is that ACC is a low-grade malignant tumor. If patients who experience local recurrence are treated promptly with salvage

treatment, they can still attain a longer OS. Furthermore, patients are prone to distant metastasis, which is also one of the typical failure patterns of ACC.^{22,31} However, RT is only a local treatment and cannot reduce the risk of distant metastasis. Therefore, the failure to treat other organs will also affect OS and DFS.

Populations Likely to Benefit From PORT

To understand which patients benefit from PORT, researchers usually use multivariate Cox regression analysis to elucidate all relevant prognostic factors.^{7,22,32–35} However, these prognostic factors are often combined with other independent factors, and surgeons and radiologists may be confused when several prognostic factors coexist. To avoid the interaction between these factors and combine prognostic factors with risk of recurrence, we initially included all relevant risk factors reported^{7,22,32–35} in the RPA model for risk stratification analysis. We then analyzed the role of PORT by

hierarchical analysis, which is different from the traditional statistical analysis methods used to date.^{3,16,19,27} RPA is one of the most successful models for stratifying patients into subgroups with homogeneous survival performance and has been performed to create prognostic algorithms for numerous malignancies.^{36,37}

As a result, these objective risk factors (surgical margins, T stage, primary tumor location, and bone invasion) were confirmed to influence LRFS significantly in certain subgroups in the RPA model. The RPA model then categorized the patients with ACC into different recurrence-risk groups according to the aforementioned factors. In further stratified analysis, we found that the benefit of PORT is more obvious in intermediate- and high-risk patients. Although the difference was non-significant in low-risk patients, they might also benefit from PORT. Larger cases and longer follow-up time are required for further study on the benefit of PORT for low-risk patients. As a result, surgeons and radiologists can screen out patients with ACC who will benefit most from PORT while providing them with sound advice on adjuvant treatment. Furthermore, some low-risk patients can avoid overtreatment and adverse effects of RT, and treatment costs will be reduced overall.

Our study had several limitations. First, this was a retrospective study and lacks the highest clinical evidence. Second, this was an 18-year study, and treatment methods and technologies are constantly changing. Moreover, the study lacked details on radiation toxicity. Therefore, prospective studies and improved follow-up strategies are necessary for further study.

Conclusions

PORT is an important factor in improving the local control of patients with ACC but did not improve DMFS, DFS, or OS. Furthermore, we found that the benefit of PORT is more obvious in intermediate- and high-risk patients, but whether low-risk patients could benefit from PORT requires further study. This can help surgeons and radiologists provide reasonable guidance on LRFS for postoperative patients.

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Role of Postoperative Radiotherapy in Nonmetastatic Head and Neck Adenoid Cystic Carcinoma

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eFigure 1: Representative Clinical Target Volume of a 33-Year-Old Woman With Adenoid Cystic Carcinoma of Parotid Gland Without Nerve Invasion

eFigure 2: Representative Clinical Target Volume of a 52-Year-Old Woman With Adenoid Cystic Carcinoma of Submandibular Gland With Nerve Invasion

eFigure 3: Kaplan-Meier Estimates of Distant Metastasis-Free Survival in Different Prognostic Groups

eTable 1: Primary Tumor Locations Among Study Cohort

eFigure 1. Representative clinical target volume of a 33-year-old woman with adenoid cystic carcinoma of parotid gland without nerve invasion (red line represents the area of the target).

eFigure 2. Representative clinical target volume of a 52-year-old woman with adenoid cystic carcinoma of submandibular gland with nerve invasion (red line represents the area of the target).

eFigure 3. Kaplan-Meier estimates of the role of PORT in DMFS in the (A) low-risk, (B) intermediate-risk, and (C) high-risk groups, derived by recursive partitioning analysis.

Abbreviations: DMFS, distant metastasis-free survival; PORT, postoperative radiotherapy.

eTable 1. Primary Tumor Locations Among Study Cohort

Primary Tumor Location	n (%)
Total, N	319
Major salivary gland	
Parotid	52 (16.3)
Submandibular	33 (10.3)
Sublingual	12 (3.8)
Minor salivary gland	
Hard/Soft palate	68 (21.3)
Floor of mouth	35 (11.0)
Buccal	33 (10.3)
Mobile tongue	15 (4.7)
Lip	15 (4.7)
Retromolar	12 (3.8)
Maxilla	8 (2.5)
Mandible	3 (0.9)
Other	
Eye socket	5 (1.6)
Maxillary sinus	5 (1.6)
Base of tongue	5 (1.6)
Nasal cavity	4 (1.3)
Oropharynx	4 (1.3)
Nasopharynx	3 (0.9)
Facial skin	2 (0.6)
Ethmoidal sinus	1 (0.3)
Paranasal sinus	1 (0.3)
Hypopharynx	1 (0.3)
Larynx	1 (0.3)
Parapharyngeal space	1 (0.3)