Single institutional experience of head and neck adenoid cystic carcinomas

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Abstract

Purpose: Aim of this study is to analyzing the outcomes of the head and neck adenoid cystic carcinomas (ACC) according to tumor stage, perineural invasion (PNI), lymphovascular invasion (LVI) and determining the risk of local failure.

Methods: The data of 68 ACC patients between 2002 and 2016 we are collected from electronic database of Gazi University Medical Faculty and patients files. Thirteen patients were excluded from study because of lack of information. Univariate Kaplan Meier and multivariate analysis Cox regression tests we are used to identify local recurrence free survival and it predictors.

Results: The mean age of study was 54.2 years. 31 patients (56.3%) had perineural invasion, 31 patients (56.3%) had stage T3-T4 disease and 9 patients (16.3%) had a positive lymph node. Mean follow-up duration was 57.7 months and 73.5% of the patients survived during this period. T stage of tumor (p=0.034), nodal status (p=0.001) and positive/close surgical margins (p=0.017) were determined as risk factors for disease free survival. However, in contrast to literature, postoperative radiation therapy (PORT) seemed insignificant the tumor control (p=0.235),because, all patients in the no PORT group were consisted of T1-2 tumors resected with wide surgical margins. So, the benefit of PORT could not be assessed properly due to the composition of groups.

Conclusion: There is an eloquent correlation between the local recurrence risk and T stage of tumor, nodal involvement and surgical margins. However, benefit of PORT could not be assessed properly, due to design of no PORT group.

Introduction

Adenoid cystic carcinomas (ACC) are one of the rarely seen head and neck malignancies which compose of 1% of total [1]. ACCs mostly arise from salivary gland epithelium and mucous glands of oral cavity. Despite their slow and indolent pattern of growth, ACCs are very aggressive tumors with high local recurrence and distant metastasis ratio. Surgery is the primary choice for treatment. However, results of some of the previous studies revealed that adjuvant radiotherapy increases the local control and survival rates when it is used in proper indications [2]. In this study, we want to report the outcomes of ACC of head and neck managed according to tumor stage, tumor site, positive margin, LVI, PNI and several other factors in our institution and compare the results of our series of ACC of head and neck with the literature.

Materials and methods

The data of 68 ACC patients between the 2002 and 2016 we collected from electronic database of Gazi University Medical Faculty and patients files. Thirteen patients were excluded from study because of lack of information. All the tumor sites originated from the head and neck region (major and minor salivary glands, palate, maxillary sinus, tongue) were included in the study. Only the patients who were treated with curative intent were selected. Treatment options were determined due to the T stage, node status and positive/close surgical margins. Neck dissection as applied to patients with T3-4 tumor or positive lymph node. Bilateral neck dissection decision as made according to tumor sites.

All the patients with T3-4 tumors, positive/close surgical margins and positive lymph node treated with adjuvant radiotherapy. Sixty Gy dose as given to the tumor bed if R0 (no residual disease) resection was made. If surgical margins close or positive, radiation dose as escalated up to 66-70 Gy for tumor bed. For the neck irradiation, 50 Gy were given to the N0 patients; 60 Gy were applied to only high risk regions. IMRT (Intensity Modulated Radiotherapy) and 3D-CRT (three dimensional conformal radiotherapy) techniques were used for radiation therapy.

Histologic subtypes, surgical margins and perineural invasion were identified by pathologic examination. Univariate Kaplan Meier analysis used to evaluate overall survival and disease free survival and multivariate Cox regression test was used to determine the significance of the risk factors for local failure.

Results

Patients’ characteristics are shown in Table 1. Seventysix percent of the patients were younger than 65 years old. Median age was 54.2.

Key words: adenoid cystic carcinomas, radiotherapy, surgery, salivary glands, head and neck

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months 73.5% of the patients survived. Surgical margins, nodal status and T stage of tumor were statistically significant predictors for 5 year disease free survival according to our data (Figure 2).

In accordance with previous studies, our results seemed similar in the aspect of prognostic indicators [6-8]. However, our study and some other studies reported the perineural invasion is not related with local recurrence [9]. Also there are some studies showing that us tumor site is an important factor for prognosis [10,11]. However, in our series of ACC, tumor site is independent from the local failure of disease.

Iseli et al recently reported data of 183 ACC cases and overall survival rates for 5 and 10 years were 68.2% and 40.8% respectively [12]. They also showed the superiority of surgery + radiotherapy for disease free survival over surgery alone or radiotherapy alone. A more actual study was published by Ali et al with very favorable local control rates 89% and 79% for 5 and 10 years respectively [13]. The study supports the efficacy of PORT for local control of ACC. Despite the literature,

| Characteristic          | n  | 5-year LRFS (%) | P Value |
|-------------------------|----|-----------------|---------|
| Age                     |    |                 |         |
| <65                     | 42 | 69.9            | 0.372   |
| >65                     | 13 | 90              |         |
| Gender                  |    |                 |         |
| Female                  | 26 | 84.2            | 0.05    |
| Male                    | 29 | 64.3            |         |
| Smoker                  |    |                 |         |
| No                      | 17 | 80.4            | 0.781   |
| Yes                     | 11 | 77.8            |         |
| Alcohol                 |    |                 |         |
| No                      | 7  | 64.3            | 0.314   |
| Yes                     | 38 | 74.1            |         |
| Site                    |    |                 |         |
| Submandibular           | 17 | 70.7            | 0.619   |
| Maxilla                 | 9  | 50              |         |
| Palate                  | 10 | 55.6            |         |
| Parotis                 | 7  | 83.3            |         |
| Other                   | 13 | 66.7            |         |
| Clinical T Stage        |    |                 |         |
| cT1-cT2                 | 24 | 94.1            | 0.011   |
| cT3-cT4                 | 31 | 64.6            |         |
| Nodal status            |    |                 | <0.001  |
| N0                      | 9  | 21.4            |         |
| N1                      | 44 | 83.5            |         |
| Perineural Invasion     |    |                 | 0.804   |
| No                      | 18 | 87.5            |         |
| Yes                     | 31 | 63.9            |         |
| Margins                 |    |                 | 0.017   |
| Negative                | 20 | 80              |         |
| Close/positive          | 26 | 56.2            |         |
| Tumor Size              |    |                 | 0.176   |
| ≤ 4 cm                  | 25 | 89.3            |         |
| >4 cm                   | 23 | 64.9            |         |
| PORT                    |    |                 | 0.235   |
| No                      | 15 | 87.5            |         |
| Yes                     | 40 | 68.7            |         |
| LVI                     |    |                 | 0.279   |
| No                      | 37 | 66.7            |         |

Male/female ratio was similar to each other, 52.7% men and 47.3% women. Only 20% of the patients were smokers, however 69% of the patients consumed mild to moderate levels of alcohol. Most of the tumors arose from the submandibular gland (30.9%). Most of the tumors were bigger than 4 cm (41.8%). 12.7% of the patients had T1, 25.4% had T2, 21.8% had T3 and 34.5% of them had T4 tumors. Eighty percentage of the patients had N0 disease. In accordance with tumor characteristics, 56.3% of the patients had PNI. However, ratio of lymphovascular invasion was only 21.8%. Relevant with big tumor sizes, most of the patients had close or positive surgical margin status (47.2%). 72.7% of the patients received PORT as adjuvant or definitive treatment. Conformal and IMRT techniques were used for radiation therapy. Postoperative tumor site, lymph node area and pathways of mandibular and facial nerves leading to the skull base were included in the clinical target volume (CTV). Nodal status, T stage of tumor and surgical margins were independent predictors of local failure. PORT is also very effective for the local control of the disease. Local failure ratio for the PORT group was only 12.5 %. It is 31.3 % for the no PORT group although, it seemed statistically insignificant due to the distribution of the cohort (Figure 1).

Discussion

ACCs of head and neck are rare but aggressive tumors which are characterized by high rates of local failure, PNI and distant metastases especially in lungs [3-5]. Due to the aggressive course of the disease and adverse effects of the surgery and PORT, treatment should be performed precisely. In this regard, we aimed to report our clinical experience about ACCs, compare it with the literature and support the proper treatment modalities for selected groups of patients in order to improve quality of life. During the median follow-up time of 57.7 months 73.5% of the patients survived. Surgical margins, nodal status and T stage of tumor were statistically significant predictors for 5 year disease free survival according to our data (Figure 2).

In accordance with previous studies, our results seemed similar in the aspect of prognostic indicators [6-8]. However, our study and some other studies reported the perineural invasion is not related with local recurrence [9]. Also there are some studies showing that us tumor site is an important factor for prognosis [10,11]. However, in our series of ACC, tumor site is independent from the local failure of disease.

Iseli et al recently reported data of 183 ACC cases and overall survival rates for 5 and 10 years were 68.2% and 40.8% respectively [12]. They also showed the superiority of surgery + radiotherapy for disease free survival over surgery alone or radiotherapy alone. A more actual study was published by Ali et al with very favorable local control rates 89% and 79% for 5 and 10 years respectively [13]. The study supports the efficacy of PORT for local control of ACC. Despite the literature,
in our study, we could not prove the benefit of PORT for local control. Main reason of these result is the patient selection for PORT in our cohort. Also we did not have any opposite group for comparing the efficacy of PORT properly. No PORT group consisted of patients which had mostly T1 staged tumor with negative lymph nodes and wide surgical margins. So, independent of PORT, recurrence risk was already low. Nevertheless, in spite of statistical insignificance, PORT group had a higher rate of 5 years disease free survival (Table 2). However, a very newly published study, Cordesmeyer et al, analyzed the data of 61 ACC patients over a period of 21 years [14]. They found there is no difference between the surgery alone and surgery combined with PORT group for OS or DFS, even in according to T stage. These results make it compulsory to choose the right candidates for radiotherapy.

In these regard, in the era of genomics, molecular profiling can be visualize for each patient and personalized therapies can be apply regarding to characteristics of the tumors. In one study concerned about molecular profiling, gold nanoparticles(GNP), ALK inhibitor crizotinib and radiotherapy were combined on mice experiment [15]. ALK mutated ACCs, injected to mice subcutaneously. Then radiotherapy alone or radiotherapy with ALK targeted GNP(via crizotinib coating) applied. Combined therapy significantly reduced the tumor volume compare to the radiotherapy alone. This result shows us GNP can be use for enhancing radiotherapy. In an another study, Ferrarotto et al, detected NOTCH1 mutation in ACC related with poor prognosis [16]. A specific monoclonal antibody targeting NOTCH1 (brontictuzumab), showed a partial response in this aggressive subtype of ACC [17]. Also gamma-secretase inhibitors are effective on the solid tumors with NOTCH1 mutations [18].

Intensity modulated proton therapy(IMPT) may be another option in the treatment of ACCs for achieving to high local control rates [19]. Proton therapy make it possible to provide maximum sparing of the adjacent normal tissue while maintaining perfect coverage of the intended target [20]. According to the physical aspects of the proton beam, it gives off most of its energy at the intended target with minimal exit dose, thereby reducing the dose to the adjacent structures [21]. In addition, there is a perceived higher radiobiological effectiveness of protons compared to photon therapy due to the protons higher linear energy transfer properties and, therefore, the potentially higher cell kills [22].

**Conclusion**

There are some contraversies between results of the studies in the literature. However, nodal status, surgical margins and T stage of tumor were detected highly correlated with local recurrence in our study. We couldn't analyze the benefit of PORT properly, because of the absence of control group. In fact, randomized prospective studies are needed to clarify the doubts about treatment of head and neck ACCs, but rarity of disease make it difficult to proceed. In future trials we may see the effectiveness of new targeted agents and radiotherapy usage concomitantly.

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