Timing and Frequency of Oropharyngeal Squamous Cell Carcinoma Recurrences after Treatment with Curative Intent

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Background The increasing number of patients under surveillance after treatment of human papillomavirus-related oropharyngeal squamous cell carcinoma (OPSCC) places a great burden on healthcare providers.

Aims/Objectives The aim of this study was to explore OPSCC recurrences in a long follow-up period: their site, frequency and timepoint after primary treatment, treatment and outcome. The secondary aim was to investigate if the recurrences are diagnosed on routine follow-up visits, and if the p16 status will have an effect on the pattern of recurrences

Material and Methods We analyzed recurrences within a 10-year follow-up period after completed curatively intended treatment among OPSCC patients in Finland treated between 2000 and 2009. Patient-, tumor-, treatment- and follow-up -related parameters were investigated.

Results Out of 495 patients with no residual tumor during the first six months, 71 (14%) were diagnosed with a recurrence, of which 47 were locoregional and 28 were treated with curative intent. Of the recurrences, 86% were diagnosed during the first 36 months after primary treatment. Only ten recurrences appeared after 36 months. The median OS after recurrence was 10.9 months.

Conclusions and Significance Routine follow-up longer over three years after treatment seems not to be effective in terms of detecting OPSCC recurrences.

Key words: Oropharynx; Cancer; Squamous cell carcinoma; Head and neck; Human papilloma virus; Follow-up

Introduction

The incidence of human papilloma virus (HPV) -related oropharyngeal squamous cell carcinoma (OPSCC) is increasing in the Western world [1] and HPV is already related to up to 60-70% of all OPSCC cases [2-4]. National guidelines in the United States recommend post-treatment surveillance every one to three months during the first year after treatment, every two to six months during the second year, every four to eight months during years three to five and yearly thereafter [2,5]. In the United Kingdom, there is a similar program with post-treatment surveillance visits at least in every two months during the first two years after treatment, every three to six months thereafter and for at least five years in all [6]. The increasing number of patients under surveillance places a huge burden on outpatient clinics although evidence supporting intensive follow-up is scarce. Reducing post-treatment follow-up visits in HPV-associated OPSCC and shortening follow-up time has been suggested [7-10]. However, this is contradictory and further data on the timing of recurrences and the effectiveness of follow-up are needed [7,8]. Avoiding unnecessary follow-up could also reduce patient burden and be cost-effective.

The aim of the study was to explore the frequency and timing of recurrences after completed treatment with curative intent, and to find out whether patients with positive and negative p16 status have a distinctive pattern of recurrence. In addition, we evaluated whether or not the recurrences were found during scheduled follow-up visits and what were the treatment options for the recurrences.

Material and Methods

We conducted a nationwide multicenter retrospective study among patients with OPSCC. The original data consisting of OPSCC patients at all five finnish university

hospitals diagnosed between January 1, 2000 and December 31, 2009 have been published previously [11]. For this study we collected details of recurrences in this patient population during a ten-year follow-up period. Patients diagnosed with invasive squamous cell carcinoma and treated with completed curative treatment were included in the study. Details on the primary tumor site, histology, p16 status, TNM classification (UICC 7th edition), stage, details of treatment (surgery and radiation therapy, definitive radiation therapy and chemoradiotherapy), distant and locoregional recurrences, follow-up time, status at last follow-up, symptoms at the time of diagnosis of recurrence and treatment after diagnosis of a recurrence were collected from the patient records. The follow-up protocol was based on Finnish guidelines, which recommend a follow-up visit every three months during the first two years of follow-up and every four to six months during the years three to five. Overexpression of the p16 protein was used as a surrogate marker for HPV involvement [3]. The disease-free interval (DFI) was defined as the period between the completion of primary treatment and detection of recurrent disease. It was analyzed as a continuous variable and categorized as 6 to 24 months, 24 to 36 months, 36 to 48 months and 48 to 60 months. The patients at risk for recurrence were calculated before the evaluation period by excluding the patients who had died or had tumor recurrence earlier in order to calculate the exact percentage of recurrences during each evaluation period. Overall survival time (OS) was defined as the period between the completion of primary treatment or secondary treatment and death of any cause. Statistics Finland provided dates of death.

In order to focus on patients who experienced a curative response to primary treatment, we excluded patients with a residual (or recurrent) tumor within 6 months after the completion of primary treatment.

. Study permission was granted, and the institutional Research Ethics Board approved the study (record number: 179/13/03/02/2013).

Statistical Analyses

IBM SPSS Statistics version 25.0 was used to analyze the data. Categorical variables were analyzed using cross-tabulation and chi-square tests. Means with standard deviation or medians with interquartile ranges (IQR) of the continuous variables were calculated depending on the normality of the data. The T-test was used when comparing groups and nonparametric tests (Kruskal-Wallis test and Mann-Whitney U-test) were used depending on the normality of the data.

Results

Study Population

A total of 674 patients were diagnosed with OPSCC during the study period. Of them, 600 patients were considered for curative intended treatment, and the treatment was completed in 564 patients. A residual tumor within 6 months after completing the primary treatment was diagnosed in 42 (7%) patients and 27 (5%) died during the first 6 months. Altogether, 495 patients had received full curatively intended treatment and were alive without a residual tumor at six months after the primary treatment, and these patients formed our study population (Figure 1). Of them, 248 (50.1%) were treated with definitive radiation therapy with or without chemotherapy, and 247 (49.1%) were treated with primary surgery with or without post-operative radiation therapy. Of the study population, 74.1% were men, the mean age at the time of diagnosis was 57.7 years (range 26-90 years), 72% were current or ex-smokers and 35% of the patients had a history of

high alcohol consumption. The p16 status was positive in 226 (46%), negative in 127 (26%) and remained unknown in 142 (29%) patients.

Timing of recurrences

During the patients´ follow-up period of 6 to 60 months, 71 (14%) recurrences were diagnosed (Figure 2). A recurrence was diagnosed in 10% of the patients with a positive p16 status, in 21% with a negative p16 status and in 15% with an unknown p16 status (p=0.011). The majority (86%) of recurrences occurred within three years (between 6 and 36 months) from completion of primary treatment. Among these recurrences, the proportions of p16 positive, p16 negative and those with unknown p16 status were 33%, 36% and 31%, respectively. The number of recurrences between 36 and 60 months after treatment was low (n=10). Of these ten patients, two (20%) recurrences were p16 positive, five (50%) were p16 negative and three (30%) patients had unknown p16 status. Only four recurrences were diagnosed after the five-year follow-up period and p16 status was negative in each of these three cases. Recurrences were diagnosed significantly more often in patients with advanced T class during the first 36 months of follow-up ($p < 0.05$). (Tables 1-4)

Site of Recurrences

Recurrences were diagnosed as locoregional in 47 (66%) patients. Of them, 28 (60%) were treated with curative intent and 19 (40%) received palliative treatment or only symptomatic treatment. No significant difference in the proportion of patients´ p16 status was observed among those patients who received treatment with curative intention for their recurrence. We noticed a tendency for the proportion of locoregional recurrences to decline and the proportion of distant recurrences to increase with time, but the difference

did not reach statistical significance. Patients over 60 years old were more likely to develop a locoregional recurrence (p=0.008), and patients with a history of smoking were more likely to develop a recurrence, especially a locoregional one (p=0.003).

Of all the 47 patients diagnosed with a locoregional recurrence, 60% had a subjective suspicion of a recurrence or a tumor-related symptom that led patient to contact the clinic and an additional follow-up visit was scheduled where the recurrence was finally diagnosed.

Disease-free Interval and Survival

The median DFI among all the patients with a recurrence was 14.1 months (IQR 8.9-26.4). Among patients with p16 positive, p16 negative and unknown p16 status, the median DFI was 18.8 months (IQR 14.5-27.8), 9.0 months (IQR 7.7-18.7) and 13.0 months (IQR 10.0-28.6), respectively (p=0.049). The median OS after treatment of a recurrence was 10.9 months (IQR 3.6-23.4). The overall two-year and five-year survival rates after recurrence were 24% and 6% respectively. Of the 31 patients who were treated with curative intent for recurrent disease, the median OS was 23.4 months (IQR 12.7-38.8) and the two-year and five-year survival rates were 48% and 13%. The median OS of patients given palliative or symptomatic treatment only was 5.6 months (IQR 2.1-11.5) and the two-year survival rate for these patients was 5%. The OS or two- and five-year survival rates after recurrence showed no difference between the p16 status groups. A recurrence was diagnosed slightly more often if the primary treatment was radiotherapy with or without chemotherapy compared to surgical treatment with or without radiation therapy (p=0.007) but we found no difference in the DFI or OS between the patient groups with different primary treatment methods.

Discussion

Several guidelines [2,5,6] recommend intensive follow-up after primary treatment of OPSCC, but the correlation between intensive follow-up and survival or disease control seems to be lacking [12]. De-escalation of follow-up protocols has been suggested by several authors [8-10], and the cost-ineffectiveness of routine follow-up has also been discussed by authors who have stated that most recurrences are found in patients with specific recurrence-related symptoms prior to diagnosis of a recurrence [13,14]. The downside of these previous studies [9,10,12-14] on follow-up is that they included squamous cell carcinoma from several head and neck subsites, making it difficult to draw conclusions on OPSCC follow-up. In our study, we focused only on OPSCC patients with greater numbers compared to previous studies. We calculated the number of patients at risk for recurrence for the whole 10 year follow-up period (6 to 24 months, 24 to 36 months, 36 to 48 months and 48 to 60 months and over 60 months) in order to discover the timing and frequency of recurrences and to evaluate the effectiveness of routine follow-up. Similarly to findings reported previously [15,16], in our series the vast majority of recurrences were also diagnosed at an early phase of follow-up and were more often locoregional. According to the recent meta-analysis DM rate is 7% among HPV-related OPSCC [17]. Curable recurrences after 36 months were rare and patients´ prognosis after recurrence was poor even among those who received curatively intended treatment for their recurrence, regardless of their p16 statuses.

In this study, we had 389 patients in the follow-up program 36 months after the primary treatment. If these patients were followed according to the recommended guidelines in the United States and the United Kingdom [2,5,6], the patients would have attended 1,167 to 3,112 scheduled visits and numerous routine imaging examinations

during the fourth and fifth year of post-treatment follow-up. We found only 10 (2.6%) recurrences diagnosed between 36 and 60 months after the primary treatment. According to our cohort, 117 to 311 scheduled visits would be needed to find one recurrence between 36 and 60 months of follow-up, which is even more than previously reported by Pagh et al [13]. In addition, at least 6 (60%) of these patients had symptoms or a subjective suspicion of a recurrence prior to diagnosis. Further, 6 (60%) of these recurrences diagnosed between 36 and 60 months of follow-up were distant and therefore not treatable with curative intent.

The small amount of recurrences after 36 months, the poor outcome after curative intended treatment for recurrence and the symptoms or suspicion of a recurrence prior to diagnosis raises question of whether the use of resources in regular follow-up programs should be reconsidered, as suggested previously by Ilmarinen et al [8]. Considering our study and previous findings [15] of smaller risk for recurrence especially after 36 months of follow-up, routine follow-up could probably be limited to 36 months unless there is a specific reason to suspect a higher risk of recurrence in selected cases. Patients should receive education on both recurrence-related symptoms and treatment related toxicities especially after radiation therapy and a low-threshold contact with an otolaryngologist in case new symptoms or suspicion of a recurrence occur.

Studies on the effect of HPV or p16 status on the survival of OPSCC patients after recurrence are contradictory. Better survival for patients with HPV-positive recurrent OPSCC compared to HPV-negative counterparts have been reported [18], but findings with no difference in survival rates have also been presented [19]. We found no difference in survival after recurrence between patients with different p16 statuses. Even though there are slightly more deaths and recurrences among patients with p16 negative

tumors, opposed to Frakes et al [7], our result does not support different follow-up protocols based on p16 status.

Despite limitations, we consider this study to have several strengths. The study was conducted nationwide in all the tertiary centers, which treat head and neck cancers in Finland, and therefore includes most of the OPSCC cases diagnosed in Finland between 2000 and 2009. All head and neck cancer recurrences are referred to one of the university hospitals for evaluation of treatment, so we consider our data to be reliable. The consecutiveness of patients minimizes the possibility of selection bias. The healthcare system in Finland is homogenous throughout the country. All the OPSCC recurrences are treated in one of the five university hospitals and therefore the risk for a missed recurrence is minimal. Because of the national social insurance system, socioeconomic factors have only a minimal impact on treatment selection. Patients' treatment plans are made in a multidisciplinary team with head and neck surgeons and oncologists. The study was conducted during a period when the proportions of p16 positive and negative OPSCC cases was changing in Finland, and therefore our cohort included a representative number of patients with both p16 positive and negative cancers. In addition, the follow-up time was longer than in previous reports [16].

The lack of p16 staining results for a subset of the patients is a limitation of this study. The study material was collected from a period when p16 staining was not routinely performed. Furthermore, the lack of HPV status determination may result in overestimation in the number of HPV-related cases. The fact that the seventh edition of the Union for International Cancer Control TNM classification was used instead of the latest eighth edition is also a weakness, as is the lack of information regarding the extracapsular growth of neck node metastasis. Due to the retrospective set-up, the availability of the data remains limited, and hence information on new symptoms or

suspicion of a recurrence is limited to patients with a diagnosed recurrence. In addition, we did not have data regarding second primary tumors, which may occur several years after the recommended follow-up period [20]. Assessing the need of follow-up in order to detect eventual second primaries is beyond this study. Although our patient series is slightly larger than many other previous series, the total number of patients with recurrences remain quite low.

Further prospective studies could shed light on shorter and symptom-based follow-up protocols. As the number of recurrences in this study was low after a three-year follow-up regardless of p16 status (Tables 1-4), a shorter three-year follow-up and low threshold for contact and new symptom-based examination by an otolaryngologist after routine follow-up should be considered in future prospective studies. The effectiveness of routine imaging examinations during follow-up after treatment should also be investigated in a prospective study.

Conclusion

Most recurrences of OPSCC seem to occur within the first 36 months after primary treatment. Curable locoregional recurrences after 36 months are rare among patients with both positive and negative p16 status. The value and effectiveness of routine follow up among OPSCC patients 36 months after primary treatment may not be useful. There is need to evaluate prospectively symptom-based follow-up protocols both before and after three years of follow-up.

Disclosure statement

The authors report there are no competing interests to declare.

References

1. de Martel C, Georges D, Bray F, et al. Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis. Lancet Glob Health. 2020 Feb;8(2):e180-e190.
2. Pfister DG, Spencer S, Adelstein D, et al. Head and Neck Cancers, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2020 Jul;18(7):873-898.
3. Prigge ES, Arbyn M, von Knebel Doeberitz M, et al. Diagnostic accuracy of p16(INK4a) immunohistochemistry in oropharyngeal squamous cell carcinomas: A systematic review and meta-analysis. Int J Cancer. 2017 Mar 1;140(5):1186-1198.
4. Koyfman SA, Ismaila N, Crook D, et al. Management of the Neck in Squamous Cell Carcinoma of the Oral Cavity and Oropharynx: ASCO Clinical Practice Guideline. J Clin Oncol. 2019 Jul 10;37(20):1753-1774.
5. Cohen EE, LaMonte SJ, Erb NL, et al. American Cancer Society Head and Neck Cancer Survivorship Care Guideline. CA Cancer J Clin. 2016 May;66(3):203-39.
6. Simo R, Homer J, Clarke P, et al. Follow-up after treatment for head and neck cancer: United Kingdom National Multidisciplinary Guidelines. J Laryngol Otol. 2016 May;130(S2):S208-S211.
7. Frakes JM, Naghavi AO, Demetriou SK, et al. Determining optimal follow-up in the management of human papillomavirus-positive oropharyngeal cancer. Cancer. 2016 Feb 15;122(4):634-41.
8. Ilmarinen T, Keski-Santti H, Markkanen-Leppanen M, et al. De-escalation of post-treatment surveillance in oropharyngeal cancer. Head Neck. 2019 May;41(5):1457-1462.
9. Kothari P, Trinidade A, Hewitt RJD, et al. The follow-up of patients with head and neck cancer: an analysis of 1,039 patients. Eur Arch Otorhinolaryngol. 2011 Aug;268(8):1191-1200.
10. Pagh A, Grau C, Overgaard J. A longitudinal study of follow-up activities after curative treatment for head and neck cancer. Acta Oncol. 2015 May;54(5):813-9.
11. Jouhi L, Halme E, Irjala H, et al. Epidemiological and treatment-related factors contribute to improved outcome of oropharyngeal squamous cell carcinoma in Finland. Acta Oncol. 2018 Apr;57(4):541-551.
12. Imbimbo M, Alfieri S, Botta L, et al. Surveillance of Patients with Head and Neck Cancer with an Intensive Clinical and Radiologic Follow-up. Otolaryngol Head Neck Surg. 2019 Oct;161(4):635-642.
13. Pagh A, Vedtofte T, Lynggaard CD, et al. The value of routine follow-up after treatment for head and neck cancer. A national survey from DAHANCA. Acta Oncol. 2013 Feb;52(2):277-84.

14. Kyto E, Haapio E, Minn H, et al. Critical review of the follow-up protocol for head and neck cancer patients. J Laryngol Otol. 2019 May;133(5):424-429.
15. Culie D, Lisan Q, Leroy C, et al. Oropharyngeal cancer: First relapse description and prognostic factor of salvage treatment according to p16 status, a GETTEC multicentric study. Eur J Cancer. 2021 Jan;143:168-177.
16. Asheer J, Jensen JS, Gronhoj C, et al. Rate of locoregional recurrence among patients with oropharyngeal squamous cell carcinoma with known HPV status: a systematic review. Acta Oncol. 2020 Sep;59(9):1131-1136.
17. Crossley JR, Nelson LL, Chou J, et al. Distant metastases in human papillomavirus-related oropharyngeal squamous cell carcinoma: Systematic review and meta-analysis. Head Neck. 2023 Jan;45(1):275-282.
18. Larsen CG, Jensen DH, Carlander AF, et al. Novel nomograms for survival and progression in HPV+ and HPV- oropharyngeal cancer: a population-based study of 1,542 consecutive patients. Oncotarget. 2016 Nov 1;7(44):71761-71772.
19. Guo T, Qualliotine JR, Ha PK, et al. Surgical salvage improves overall survival for patients with HPV-positive and HPV-negative recurrent locoregional and distant metastatic oropharyngeal cancer. Cancer. 2015 Jun 15;121(12):1977-84.
20. Coca-Pelaz A, Rodrigo JP, Suarez C, et al. The risk of second primary tumors in head and neck cancer: A systematic review. Head Neck. 2020 Mar;42(3):456-466.

Table 1. Frequency and timing of OPSCC recurrences in p16 positive patients

N=Number of patients at risk for recurrence at specific evaluation period

Table 2. Frequency and timing of OPSCC recurrences in p16 negative patients.

N=Number of patients at risk for recurrence at specific evaluation period

Table 3. Frequency and timing of OPSCC recurrences in patients with unknown p16 status. N=Number of patients at risk for recurrence at specific evaluation period, *=$p<0.05$

Table 4. Frequency and timing of OPSCC recurrences in all the patients. N=Number of patients at risk for recurrence at specific evaluation period,*=$p<0.05$

Figure 1. Flow chart of the study.

Figure 2. Timing and frequency of locoregional, distant and all recurrences.