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Impact of delayed adjuvant therapy after surgery in p16 positive oropharyngeal cancer: a retrospective analysis

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Abstract. – OBJECTIVE: This study aimed to clarify the impact of delayed adjuvant therapy on the outcome of HPV associated oropharyngeal squamous cell carcinoma (HPV-OPSCC).

PATIENTS AND METHODS: A total of 157 patients with HPV-OPSCC treated by surgery and adjuvant radiotherapy or chemoradiation therapy were analyzed retrospectively. We divided participants into two groups implementing adjuvant therapy within or after 50 days. Primary endpoints were the rates of locoregional recurrence and distant metastases, overall survival, and disease-specific survival.

RESULTS: Adjuvant treatment began within 50 days (average: 38.8 days) in 79 cases compared to 78 cases after 50 days (average: 71.5 days). Five-year overall survival was 85.7% and 87.4% (p=0.588), the rates of local and regional recurrence were 3.8% and 6.4% (*p*=0.455) and of distant metastases 5.1% and 9% (*p*=0.369) implementing adjuvant treatment within or later than 50 days, respectively.

CONCLUSIONS: These results suggest that adjuvant therapy initiated later than seven weeks after primary ablative surgery may still be effective HPV-OPSCC.

Key Words:
HPV associated oropharyngeal cancer, Delayed adjuvant treatment, Primary ablative surgery, Head and neck cancer, p16 positivity.

Introduction

The incidence of oropharyngeal squamous cell carcinoma (OPSCC) is rising in the last decades due to an increased number of infections with oncogenic human papillomavirus (HPV)[1,2]. Epidemiological data shows that HPV associated OPSCC (HPV-OPSCC) is diagnosed more frequently in young patients without extensive use of tobacco or alcohol[3]. The prevalence of HPV-OPSCCs among all diagnosed OPSCCs is reported to be between 35-80% in Western countries[4,5] and up to 34% in Asia[6].

In early-stage OPSCC, therapeutic options recommend primary surgical tumor removal or radiotherapy (RT) as a single treatment modality[7]. Treatment recommendations for advanced stage OPSCC suggest either primary chemoradiation therapy (RCT) or primary surgery followed by risk-adapted RT/RCT[8]. Both primary radiation and primary surgery proved to be effective therapeutic options[9]. Further indications for postoperative adjuvant therapy include advanced tumor stages, insufficient surgical resection margin, two or more regional lymph node metastases, or the presence of extracapsular nodal spread[10-12]. Based on the present state of knowledge, HPV-OPSCC is associated with favorable treatment response and relatively high cure rates compared to non-HPV-OPSCC[5,13-15].

Regarding the time point, Chen et al[16] generally recommended the implementation of adjuvant therapy for head and neck carcinomas within six weeks after primary surgery. In general, a delay of therapy of more than six weeks is assumed to have a negative impact on the outcome[16-18].

Ablative surgery of advanced stage OPSCC is associated with postoperative complications of various degrees. Accordingly, the development of complications, such as prolonged wound healing or the presence of numerous comorbidities leading to prolonged intensive care treatment. Thus, an extended time to recovery may impede the initiation of the appropriate adjuvant therapy[19].

This study aimed to evaluate the effect of delayed adjuvant therapy on the oncologic outcome in patients with HPV-OPSCC undergoing primary surgery, followed by risk-adapted adjuvant treatment.

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Patients and Methods

Study Design

We conducted this retrospective study at a tertiary hospital and academic cancer center. Approval was given by the Local Institutional Ethics Committee and carried out following the Declaration of Helsinki.

Eligibility Criteria

All patients diagnosed with HPV-OPSCC that were treated by surgical tumor removal followed by appropriate adjuvant therapy, i.e., either RT or RCT, were retrospectively analyzed. Patients treated between January 1st, 2000, and December 31st, 2016, were included. We confirmed the association with HPV by overexpression of the surrogate marker p16INK4a. Treatment was primary ablative surgery, including resection of the primary tumor and neck dissection of the appropriate nodal basins. The exclusion criterion was the previous head and neck radiation.

Characteristics of Adjuvant Therapy

Our certified interdisciplinary tumor board decided on initial and adjuvant treatment modality. We performed adjuvant RT in patients with ≥ T3 disease, close resection margin (< 5 mm), lymph node metastases without extracapsular nodal spread, lymphovascular invasion, or perineural invasion. Patients with T4 disease, positive margins, ≥ 3 lymph node metastases, and the presence of extracapsular nodal spread received concomitant chemotherapy. Treatment was not de-escalated in case of HPV-positivity. Radiation techniques included 3D conformal radiation therapy, intensity-modulated radiation therapy, and volumetric modulated arc therapy. The dosage of radiation was 61 Gray (SD=10.7) in the primary tumor region and 52.3 Gray (SD=9.3) in the corresponding lymph node levels. We performed concomitant chemotherapy with 5-Fluorouracil in combination with Cisplatin or Carboplatin. The median duration from primary surgery to the beginning of adjuvant treatment was 50 days. We matched all patients into two groups based on the median. Patients to whom adjuvant treatment was implemented within the first 50 days after ablative surgery, in the following, referred to as "group ≤ 50 d". In contrast, patients to whom adjuvant therapy was administered later than 50 days following surgery referred to as "group > 50 d".

Outcome Parameters

Recurrence of disease was defined as local and regional tumor recurrence or distance metastases. We evaluated clinical outcomes by the estimation of the overall survival and disease-specific survival. The survival time was calculated from the date of surgery to the date of death from any cause (overall survival) or disease (disease-specific survival) or the date the patient was last known to be alive (overall survival and disease-specific survival) or dead not caused by disease (disease-specific survival). We censored patients who were still alive at the time of the follow-up cut-off.

Statistical Analysis

Patients' characteristics, as well as time values and radiation dose, are presented in mean and standard deviation (SD). Frequencies of oncological parameters and treatment modality are presented in absolute and relative values. Patients' characteristics, oncological parameters, and treatment characteristics between group ≤ 50 d and > 50 d are compared with the Chi-square-test or Mann-Whitney-*U*-test. Exact Fischer-test and Chi-square-test compared the rate of local/regional recurrence and distant metastasis between group ≤ 50 d and > 50 d. Survival rates in both groups were created by using the Kaplan-Meier-method and compared by the log-rank test. Overall and disease-specific survival values are presented in Kaplan-Meier estimate and 95% confidential interval (CI). A *p*-value of less than 0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics, version 25.0 (IBM Corp., Armonk, NY, USA).

Results

Study Cohort

A total of 1594 patients with OPSSC were treated at our Department between January 1st, 2000, and December 31st, 2016. Out of these, 157 (9.8%) were p16 positive, indicating HPV-infection. All patients referred to primary surgery, followed by adjuvant RT/RCT. We included a total of 110 men (average age of 59.8 years ± 9.6 SD) and 47 women (59 years ± 8.9 SD). The 8th version of the UICC[14] determined the pathological stage for HPV-OPSCC. Out of the 157 patients UICC stage I was found in 121 cases (77.1%), UICC II in 31 cases (19.7%), and UICC III in five cases (3.2%). In the absence of distant metastasis at the point of diagnosis, there was no UICC stage IV (Table I).

Table I. Patients' characteristics and oncological parameters for all patients and groups of patients divided based on the implementation of adjuvant therapy within (≤ 50 days) and later than (> 50 days) days after surgery.

	Group ≤ 50 days (n = 79)	Group > 50 days (n = 78)	All patients (n = 157)	Statistical comparison of patient groups ≤ 50 d vs. > 50 d *p*-value
Gender (n, %)				
Male	58 (73.4%)	52 (66.7%)	110 (70.1%)	0.454
Female	21 (26.6%)	26 (33.3%)	47 (29.9%)	
Age (mean years ± SD)	60 ± 9.5	59.0 ± 9.3	59.5 ± 9.4	0.536
Time span T_{S-Adj}. (mean days ± SD)	38.8 ± 8.3	71.5 ± 19.5	55 ± 22	<0.001
Tumor stage (n, %)				
T1	27 (34.2%)	30 (38.5%)	57 (36.3%)	0.695
T2	43 (54.4%)	37 (47.4%)	80 (51%)	0.473
T3	6 (7.6%)	7 (9%)	13 (8.3%)	0.981
T4	3 (3.8%)	4 (5.1%)	7 (4.5%)	0.791
T1 & T2				
T3 & T4	70 (88.6%)	67 (85.9%)	137 (87.3%)	0.787
	9 (11.4%)	11 (14.1%)	20 (12.7%)	
Nodal status (n, %)†				
N0	10 (12.7%)	13 (16.7%)	23 (14.7%)	0.750
N1	54 (68.3%)	55 (70.5%)	109 (69.4%)	
N2	11 (13.9%)	9 (11.5%)	20 (12.7%)	
UICC stage (n, %)				
I	62 (78.5%)	59 (75.6%)	121 (77.1%)	0.400
II	13 (16.5%)	18 (23.1%)	31 (19.7%)	0.815
III	4 (5.1%)	1 (0.1%)	5 (3.2%)	0.367
I	62 (78.5%)	59 (75.6%)	121 (77.1%)	0.815
II & III	17 (21.5%)	19 (24.4%)	36 (22.9%)	
Extranodal extension (n, %)‡				
Positive	29 (44.6%)	25 (39%)	54 (41.9%)	0.645
Negative	36 (55.4%)	39 (60.9%)	75 (58.1%)	
Resection status (n, %)				
R0	70 (88.6%)	75 (96.2%)	145 (92.4%)	0.139
R+ & Rx	9 (11.4%)	3 (3.9%)	12 (7.6%)	
Noxious agents				
Smoking	35 (44.3%)	39 (50%)	74 (47.1%)	0.579
Alcohol	52 (65.8%)	41 (52.6%)	93 (59.2%)	0.415
Medical history				
Cardiovascular diseases	11 (13.9%)	7 (9%)	18 (11.5%)	0.453
Pulmonary diseases	3 (3.8%)	1 (0.1%)	4 (2.5%)	0.620
Diabetes mellitus	9 (11.4%)	5 (6.4%)	14 (8.9%)	0.415

Abbreviations: Group ≤ 50 d = adjuvant treatment was implemented within the first 50 days after ablative surgery; Group > 50 d = adjuvant treatment was implemented later that 50 days following surgery; TS – Adj. = time from surgery to adjuvant therapy (radiotherapy/chemoradiation); SD = standard deviation; UICC = International Union Against Cancer; R+ = positive margin; Rx = no valid information of resection status.
† no ND in 3.2%, n = 5; ‡ only pathological positive lymph nodes, n = 129.

Definition of Subgroups

All patients were treated with primary surgery, including transoral tumor resection in 116 patients (73.9%) and transcervical or combined approach with simultaneous microvascular reconstruction in 41 patients (26.1%). Adjuvant RT and RCT were performed in 62 (39.5%) and 95 (60.5%) of all patients, respectively. Regarding all patients, we initiated adjuvant therapy on average 55 days after surgery (SD=22; median=50.5 days; 95% CI 51.6-58.5).

Table II. Treatment characteristics for all patients and groups of patients divided based on the implementation of regarding to the start of adjuvant therapy within (in ≤ 50 days) and later than (> 50 days) days after surgery.

	Group ≤ 50 days (n = 79)	Group > 50 days (n = 78)	All patients (n = 157)	Statistical comparison of patient groups ≤ 50 d vs. > 50 d *p*-value
Surgical treatment modality (n, %)				
Transoral approach†	56 (70.9%)	60 (76.9%)	116 (73.9%)	0.497
Transoral/Transcervical approach‡	23 (29.1%)	18 (23.1%)	41 (26.1%)	
Adjuvant treatment modality (n, %)				
Radiotherapy	27 (34.2%)	35 (44.9%)	62 (39.5%)	0.227
Radiochemotherapy	52 (65.8%)	43 (55.1%)	95 (60.5%)	
Radiation dose in Gy,				
Tumor: overall dose (mean ± SD) §	62.5 ± 7.8	59.4 ± 12.8	61 ± 10.7	0.148
Corresponding lymph drainage region:				
Overall dose (mean ± SD) ¶	53 ± 6.3	51.5 ± 11.3	52.3 ± 9.3	0.729
Chemotherapy (n, %)				
Cisplatin/Carboplatin+5-FU	32 (61.5%)	35 (81.4%)	67 (42.7%)	0.430
Other	20 (38.5%)	8 (18.6%)	28 (17.8%)	

Abbreviations: Group ≤ 50 d = adjuvant treatment was implemented within the first 50 days after ablative surgery; Group > 50 d = adjuvant treatment was implemented later that 50 days following surgery; SD = standard deviation; † including transoral laser microsurgery, transoral robotic surgery, transoral conventional surgery; ‡ combined approach with following microsurgical flap reconstruction; Gy = Gray; 5-FU = 5-Fluorouracil; § valid information, n = 154; ¶ valid information, n = 143.

The mean follow-up time was 57.6 month (SD=42) and the median time 52.8 month (95% CI 50.4-63.6). The group ≤ 50 d consisted of 78 patients (49.7%) compared to 79 patients (50.3%) of the group > 50 d. On average, adjuvant therapy was started 38.8 days (SD=8.3) after surgery in group ≤ 50 d in contrast to 71.5 days (SD=19.5) after surgery in group > 50 d ($p<0.001$). Both patient groups did not differ significantly with respect to gender ($p=0.454$), age ($p=0.536$), cardiovascular diseases ($p=0.453$), pulmonary diseases ($p=0.620$), diabetes mellitus ($p=0.415$), history of smoking ($p=0.579$) and alcohol consumption ($p=0.415$), stage of disease ($p=0.815$), nodal status ($p=0.750$), resection status ($p=0.139$), extracapsular nodal spread ($p=0.645$), modality of surgery ($p=0.497$) and adjuvant therapy ($p=0.227$), regime of chemotherapy ($p=0.430$), overall radiation dose applied to the tumor ($p=0.148$) and corresponding lymph drainage region ($p=0.729$) (Tables I and II).

Recurrence Rate

In total, 13 out of 157 patients (8.3%) revealed a recurrence averaging 27.6 month (SD=39.6) after initial surgery. Three out of 78 patients (3.8%) of group > 50 d developed a local recurrence after 16.6 month (SD=9.9). In contrast there was no local recurrence in group ≤ 50 d. Two out of 78 patients (2.6%) developed regional recurrence in group > 50 d in average 6.5 months (SD=4) after surgery, compared to three out of 79 patients (3.8%) of group ≤ 50 d that developed regional recurrence in average after 12.7 month (SD=9). Thus, local and regional recurrence in group > 50 d (n=5; 6.4%) was not significantly different from group ≤ 50 d (n=3; 3.8%; $p=0.455$). Distant metastasis occurred in seven out of 78 patients (9%) after 68.5 months (SD=44.2) in > 50 d group and four out of 79 patients (5.1%) after 94.6 months (SD=78.8) in group ≤ 50 d ($p=0.369$) (Table III).

Survival Rate

Regarding all patients, the 5-year overall survival was 88% (95% CI 0.82-0.94). The overall survival was 85.7% (95% CI 0.76-0.96) and 87.4% (95% CI 0.78-0.96) in the group ≤ 50 d and > 50 d, respectively ($p=0.588$; Figure 1).

The disease-specific survival of all patients included was estimated with 97.4% (95% CI 0.94-1). The disease-specific survival was 96.1 % (95% CI 0.9-0.96) and 98.6 % (95% CI 0.96-1) in group ≤ 50 d and > 50 d exhibiting no significant difference ($p=0.536$; Figure 2). Survival rates are shown in Table III.

Table III. Rate of recurrence, disease specific survival and the overall survival for all patients and groups of patients divided based on the implementation of adjuvant therapy within (≤ 50 days) and later than (> 50 days) days after surgery.

		Group ≤ 50 days n (%)	Group > 50 days n (%)	All patients n (%)	Statistical comparison of patient groups ≤ 50 d vs. > 50 d *p*-value
Recurrence of disease					
Local		0 (0%)	3 (3.8%)	3 (1.9%)	0.120
Regional		3 (3.8%)	2 (2.6%)	5 (3.2%)	>0.99
Local & Regional		3 (3.8%)	5 (6.4%)	8 (5.1%)	0.455
Distant metastasis		4 (5.1%)	7 (9%)	11 (7%)	0.369
5-year-DSS	events:	2 (1.3%)	1 (0.6%)	3 (1.9%)	0.536
(KM Estimate; 95% CI)		0.961; 95% CI (0.9-0.96)	0.986; 95% CI (0.96-1)	0.974; 95% CI (0.94-1)	
5-year-OS	events:	9 (11.4%)	13 (16.7%)	22 (14%)	0.588
(KM Estimate; 95% CI)		0.857; 95% CI (0.76-0.96)	0.874; 95% CI (0.78-0.96)	0.880; 95% CI (0.82-0.94)	
In total					
n (%)		79 (50.3%)	78 (49.7%)	157 (100%)	

Abbreviations: Group ≤ 50 d = adjuvant treatment was implemented within the first 50 days after ablative surgery; Group > 50 d = adjuvant treatment was implemented later that 50 days following surgery; DSS = disease-specific survival; OS = overall survival; KM = Kaplan-Meier.

Discussion

The results of this study support the known favorable oncologic outcome of HPV-OPSCC. In particular, the results demonstrate that a prolonged time between surgery and the initiation of adjuvant therapy of more than 50 days did not significantly compromise the rate of local and regional recurrence. Furthermore, we found no impact on distant metastases in this investigated cohort. However, timely initiation of adjuvant therapy is considered an essential factor to avoid repopula-

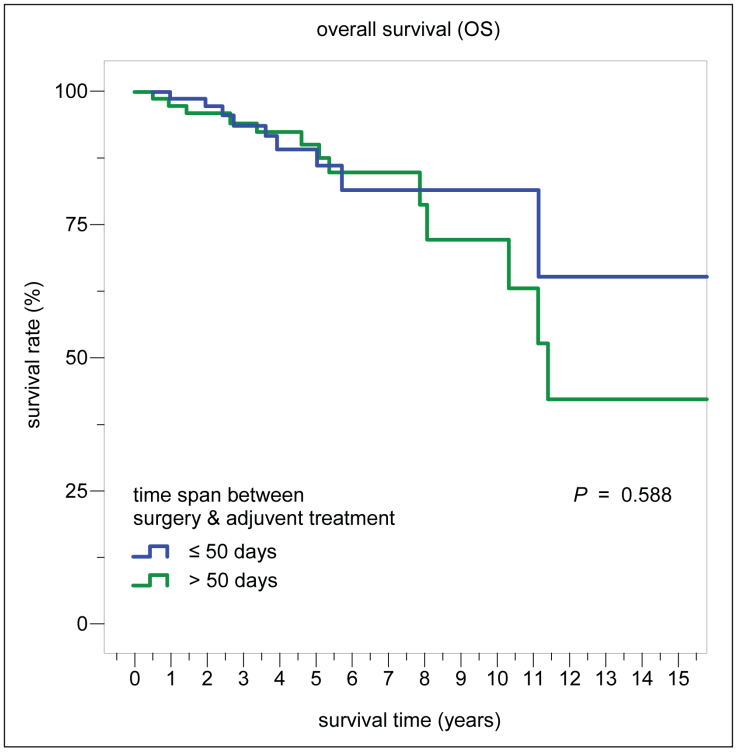

Figure 1. Association of time span from surgery to adjuvant therapy with overall survival. Kaplan-Meier estimates of overall survival according to the implementation of adjuvant therapy within (≤ 50 days) and later than 50 days (> 50 days) after surgery (p=0.588).

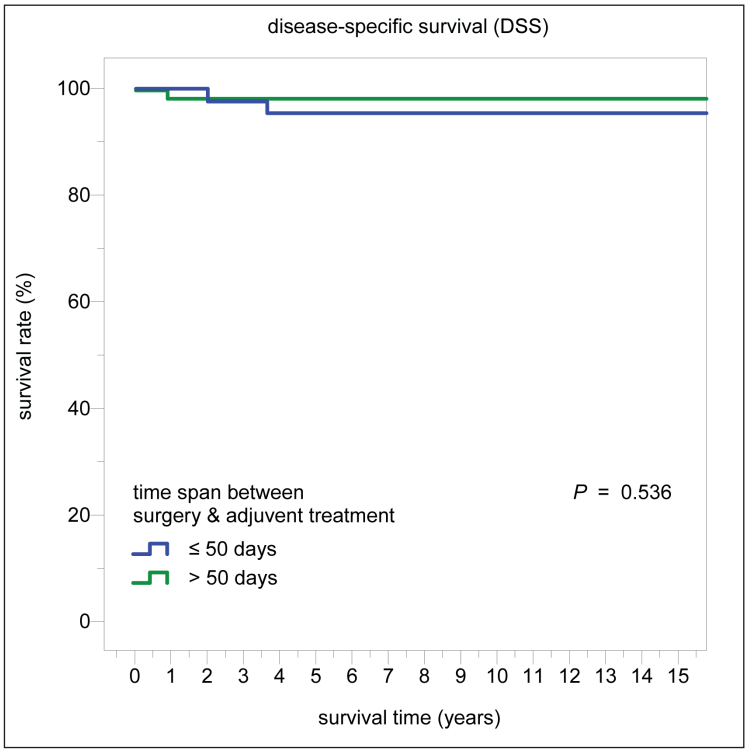

Figure 2. Association of delay from surgery to adjuvant therapy with disease-specific survival. Kaplan-Meier estimates of disease-specific survival according to the implementation of adjuvant therapy within (≤50 days) and later than 50 days (>50 days) after surgery (p=0.536).

tion of residual malignant cells and to increase the efficacy of adjuvant treatment[12,20,21]. Thus, the beginning of adjuvant therapy within a time frame of six weeks has been recommended[12,16,18,22]. The prevailing opinion is that the risk of locoregional recurrence is higher among patients that started radiotherapy later than six weeks after surgery compared to those with earlier radiotherapy[16,17,23].

Kajanti et al[24] demonstrated a significant association of the overall survival with 61%, 46%, and 30% for patients treated at 1-6 weeks, at 7-8 weeks, and at more than eight weeks after surgery, respectively. Ang et al[11] reported that a prolonged interval between surgery and radiation of more than seven weeks was associated with significantly lower local control rate and survival rates in patients with high-risk head and neck squamous cell carcinoma (HNSCC). Besides, a therapy duration of more than 11 weeks has a negative influence on the local control rate. Chen et al[16] conducted a meta-analysis of 14 studies, including 5091 patients with HNSCC. In conclusion, there was a "marginally significant" decrease in overall survival combined with increasing periods for adjuvant therapy (relative risk death/month=1.16, 95% CI 1.02-1.32). In a retrospective analysis, based on National Cancer Database, Harris et al[17] describe an inferior overall survival in patients with tonsil-OPSCC (hazard ratio 1.20; 95% CI 1.05-1.36) and non-tonsil-OPSCC (hazard ratio 1.38; 95% CI 1.19-1.59) depending on the initiation of adjuvant therapy within 42 days or less and 50 days or more.

In contrast, Bastit et al[25] published a retrospective analysis of 420 patients with oropharyngeal and hypopharyngeal cancer. Patients received adjuvant radiotherapy within and after 30 days following primary surgery. There was no significant beneficial effect of early adjuvant therapy on overall survival and local recurrence. However, none of the reports mentioned above stratified the results concerning HPV infection. This limits the comparison of these studies to the presented results. HPV-OPSCC is considered as a distinct tumor entity that exhibits favorable oncologic outcomes following adjuvant therapy[5,13-15]. Chao et al[15] evaluated the treatment package time (timespan from surgery to completion of adjuvant treatment) on its impact on locoregional control in a cohort of 267 HPV-OPSCC. The authors stated a decreased locoregional control rate while increasing the total package time from 13 to 15 weeks. However, no differences were reported at the cut-off package time of 15 weeks. Besides, Townsend et al[18] reported no significant influence of therapy initiated between 6 and 8 weeks after surgery and overall treatment time of more than 100 days on overall survival and recurrence-free survival in HPV-OPSCC. Accordingly, these results are in line with the presented study. They indicate that delayed adjuvant

therapy of HPV-OPSCC is still effective concerning locoregional control and overall survival. Thus, treatment time dependency of HPV-OPSCC seems to be less crucial compared to non-HPV-OPSCC. These results support our conclusion that a delayed adjuvant RT/RCT does not appear to have a negative influence on overall survival in HPV-OPSCC. Based on the presented results and literature, we can assume that the influence of therapy delays on the outcome of HPV-OPSCC differs from that of non-HPV associated tumors.

The diagnosis of HPV associated OPSCC was based on the immunohistochemical assay of p16INK4a in accordance with the current version of UICC[14]. Its sensitivity and specificity are reported to be reasonably high at 94% and 83%, respectively[26]. However, that lack of accuracy limits its value as a surrogate parameter for HPV positivity.

Of note, the presented results need to be interpreted, considering the retrospective character. However, our cohort included every patient with HPV-OPSCC treated in our department between 2000 and 2016, giving rise to two patient groups with a similar distribution of relevant oncological parameters reducing the inevitable selection bias. The results should be considered given the relatively small number of recurrences and disease-specific events. This affects the accuracy of the estimation of disease-specific survival. Still, a prospective randomized trial investigating a treatment delay is ethically unacceptable. Despite the presented results, the identification of a definite threshold time point between ablative surgery and adjuvant therapy and its impact on local recurrence and survival rates were beyond the scope of this study but surely warranted further research on this crucial topic.

Focusing on HPV-OPSCC the presented results indicate that a time of more than 50 days before the implementation of adjuvant therapy may not adversely affect the survival of patients. Thus, the generally recommended "therapeutic window" may be enlarged without adverse effects on the oncological outcome.

Conclusions

In HPV-OPSCC, implementation of adjuvant therapy following ablative surgery later than 50 days did not exhibit significant adverse effects on overall survival, locoregional tumor control, and distant metastases. Thus, the results indicate that patients with HPV-OSCC may still benefit from delayed initiation of adjuvant therapy.

Ethical Approval

All procedures performed in this study involving human participants were following the ethical standards of the Institutional and National Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Ethical approval (approval number 394_18Bc) was given by the Non-Intervention Clinical Research Ethics Committee of the Medical Faculty (Friedrich Alexander University of Erlangen-Nuremberg, Germany).

Informed Consent

A formal informed consent procedure was waived due to the retrospective nature of this study.

Conflict of Interests

All authors declare that they have no financial support or relationship that may pose a conflict of interest.

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