Clin Oral Invest (2004) 8:56–62
DOI 10.1007/s00784-003-0246-z

ORIGINAL ARTICLE

Franz-Josef Kramer · Marcel Janssen · Andre Eckardt

Second primary tumours in oropharyngeal squamous cell carcinoma

Received: 28 April 2003 / Accepted: 18 November 2003 / Published online: 16 March 2004

Abstract Improved diagnostic techniques and more effective treatment concepts have resulted in a growing number of patients with oropharyngeal cancer diagnosed with second primary tumours. In order to evaluate the relative number of patients with second primary tumours and to estimate the efficacy of diagnostic procedures, a retrospective evaluation of 981 patients with oropharyngeal cancer, who were treated during 20 years in one single medical centre, was performed. In total, 9.2% of the patients were affected by secondary cancer, 1.5% from tertiary cancer and 0.2% from quartary cancer. Of the multiple cancers, 27.8% occurred synchronously and 72.2% metachronously. If the index tumour was located at the oral floor or the pharynx, the risk of second primary tumours was enhanced; if the index tumour was located at the lips or the tongue, the risk was reduced. The 5-year survival of all examined patients was 34.1%; the survival of patients with multiple cancers was 62.3% at the diagnosis of the index tumour and dropped to 30.5% at the diagnosis of an additional malignancy. Of the second primary tumours, 23.2% were diagnosed by panendoscopy. We conclude that among patients with oropharyngeal cancer, the presence of second primary tumours always has to be considered and that panendoscopy is a valuable tool for their diagnosis.

Keywords Second primary tumours · Oral squamous cell carcinoma · Panendoscopy · Oropharynx · Epidemiology

Introduction

Since the early reports of Warren and Gates in 1937 [31], second primary tumours have to be understood as frequent observations. Slaughter [25, 26] already expressed in his theory of field-cancerisation that the formation of oropharyngeal cancer often is not limited to a small local process, but to a confluence of several affected areas each consisting of single local malignancies. Also at present, the incidence of second primary tumours of the upper aerodigestive tract in patients being treated for oropharyngeal cancer is a well-known clinical phenomenon. Because of improved diagnostic approaches and more effective cancer therapy strategies in recent years, the incidence of second primary tumours has become increasingly relevant to daily clinical practice.

The overall prognosis of patients suffering from oropharyngeal carcinoma has not improved during the last decades [3]. It is well known that the incidence of second primary tumours is related to a reduced prognosis of affected patients. However, in the literature a high variance is documented regarding the incidence of second primary tumours, which is between 1 and 28% [3, 10, 15, 19, 20] for patients suffering from oropharyngeal squamous cell carcinoma. These confusing data can probably be explained by regional, but also methodical divergences such as the study design and the period of post-therapeutic follow-up. Interestingly, also the reported relation of synchronous to metachronous incidences of multiple cancers varies to a great extent between 1:3 [24] and 2:1 [32]. The relevance of panendoscopy as a routine diagnostic procedure to detect synchronous multiple cancer in patients with oropharyngeal cancer is controversial. Therefore, the aim of this clinical retrospective study was twofold:

a) to determine epidemiologically the numbers of affected patients suffering from oropharyngeal carcinoma and multiple cancer
b) to identify clinical parameters that were associated with the development of multiple cancer

F.-J. Kramer (✉) · M. Janssen · A. Eckardt
Department of Oral and Maxillofacial Surgery,
Medical University of Hanover,
Carl-Neuberg-Str.1, 30625 Hannover, Germany
e-mail: Kramer.Franz@mh-hannover.de
Tel.: +49-511-5324756
Fax: +49-511-5324740

Patients and methods

The incidence, phenotype and survival rate of 981 (733 males, 74.7%; 248 females, 25.3%) consecutive patients with oropharyngeal squamous cell carcinoma who were treated between 1981 and 1999 at the Medical University of Hanover, Germany, were investigated retrospectively by chart analysis and assessed statistically. Second primary tumours were defined as by Warren and Gates [31] and Lefor et al. [11]; the criteria for second primary tumours were as follows:

a) each single tumour had to be classified histologically as malignant
b) each tumour had to be separated from another by non-malignant tissue
c) the tumour was no metastasis of the index tumour

Exclusively patients with histologically diagnosed squamous cell index carcinoma of the oropharynx were analysed. The patients' records were analysed in order to determine the relevance of several clinical and non-clinical variables. The sex (male/female) and age of the patient were documented and categorised.

The localisation of the index carcinoma was categorised according to the international classification of diseases (ICD) of the WHO into nine categories: lips, oral cavity, oral floor, tongue, pharynx, larynx, oesophagus, trachea and others. The time interval between the diagnosis of the index carcinoma, the diagnosis of an additional malignancy and loss of control and death of the patient was assessed in periods of half years or years.

Second primary tumours were described as synchronous if they were diagnosed within 6 months after the index carcinoma and as metachronous if they were diagnosed later. Simultaneous second primary tumours were diagnosed at the same time as the index tumour [13]. For staging of the patients, the TNM system of the UICC was applied [28]. If accessible, the postoperative histopathological diagnosis was preferred to the preoperative clinical diagnosis for staging.

Panendoscopy was performed both by otolaryngologists and maxillofacial surgeons. It included microlaryngoscopy, bronchoscopy esophagoscopy and inspection of the epipharynx.

Therapy concepts of the index carcinoma were classified into surgery, radiation therapy, chemotherapy, immune therapy, combinations of those and no therapy. Surgical therapy was divided into subscales including excision of the tumour, resection of the tumour, tumour resection combined with partial or complete mandibular resection, and tumour resection combined with circular resections. Non-surgical treatment concepts were subscaled in pre- or postoperative concepts, concepts without (curatively intended) operations and palliative concepts.

The reasons of death in patients with second primary tumours were classified into tumour-related reasons, non-tumour-related reasons, not clearly tumour-related reasons and unknown reasons.

Statistic evaluation of the patient data was performed with SPSS, version 10.0. Patient survival was calculated by Kaplan-Meier analysis; only patients with tumour-related death were classified as non-censored. Patients alive or who died for other reasons or who were lost from follow-up were classified as censored patients. Because of the small number of patients with second primary tumours, further statistic analysis was ignored.

Results

In total, 981 patients with previously untreated oropharyngeal squamous cell carcinoma were investigated. The average follow-up of patients with second primary tumours was 4.1 years and maximal follow-up extended up to 9.5 years. More than 86% of those patients were under follow-up for more than 2 years. In total, 90 patients (9.2%) developed second primary tumours. The average age at the diagnosis of the index tumour was 56.1 years in male patients (min. 24 years, max. 94 years) and 61.6 years in female patients (min. 19 years, max. 89 years). Of the 90 patients with second primary tumours, 66 patients were male (73.3%) and 24 were female (26.7%). The average age at the diagnosis of the index carcinoma was 55.6 years (males 55.3 years; females 56.6 years). The youngest male patient was 37 years old, and the youngest female patient was 39 years old. Of the 90 patients with second primary tumours, 75 (83.3%) developed secondary cancer, twelve (13.3%) developed secondary and tertiary cancer and three (3.3%) patients developed four independent malignancies. The preferred age at the diagnosis of an additional malignancy was, for both sexes, between 40 and 70 years. Between 1981 and 1999, the calculated relative distribution of an index or single carcinoma was 49 patients per year. For secondary cancer the relative distribution was 4.5 patients per year; for tertiary cancer it was 0.75 per year and for quartary cancer it was 0.15 per year.

The preferred anatomic localisations of single or index carcinomas in all examined patients were the oral floor, oral cavity and tongue (Fig. 1a), which were affected in more than 85% of all patients. In patients with second primary tumours, the preferred location of the index tumour was the oral floor, which was affected in approximately every second patient. Oral cavity and tongue were less frequently affected (Fig. 1b). The preferred anatomic localisations of additional malignancies included pharynx, tongue and oral floor in secondary cancer, pharynx in tertiary cancer and trachea in quartary cancer (Fig. 1c, d). Patients developing pulmonary cancer were lost of control.

Usually, additional malignancies were located more caudal than the index carcinoma. When the tumours were categorised into a cranial-anterior group (lip, oral cavity, tongue and oral floor) and a caudal-posterior group (pharynx, larynx, oesophagus and trachea) and a ratio (R) of those groups was calculated, this ratio dropped from the index tumours R=6.5 (78:12) to secondary cancer R=1 (45:45) and to tertiary cancer R=0.17 (2:12).

More than 60% of all second primary tumours were diagnosed during continuous follow-up examinations, and more than 23% by panendoscopy. In simultaneous second primary tumours, nearly every second additional cancer was diagnosed by panendoscopy (Fig. 2). Additionally, in 27.8% of all patients in follow-up, leukoplakia was diagnosed and in several others dysplasia, erosive inflammation and lichen ruber were diagnosed. The prognosis of patients with oropharyngeal carcinoma was markedly influenced by the presence of metastasis or tumour recurrence. Of the patients with second primary tumours, 45.6% had no metastasis or tumour recurrence; 22.4% of the patients developed a recurrence of the second primary tumour without metastasis, and in 21.1% metastases were diagnosed without tumour relapse. In 8.9% of the patients with second primary tumours, both

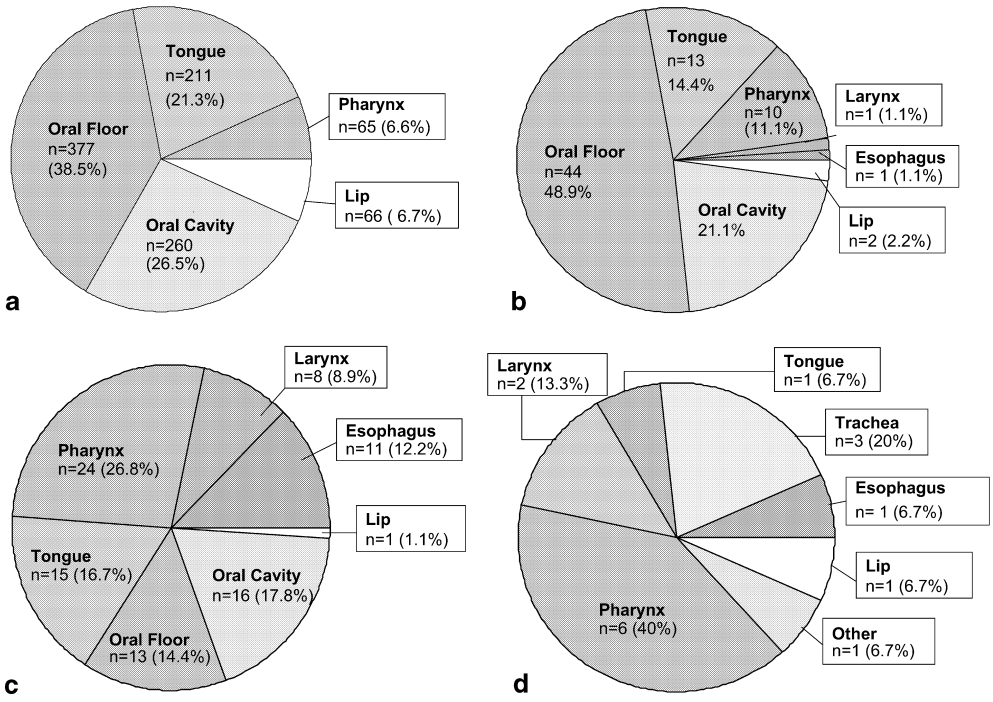


Fig. 1. a Anatomic distribution of single or index carcinoma in all patients (n=981). **b** Anatomic distribution of index carcinomas of patients developing second primary tumours (n=90). **c** Anatomic distribution of secondary cancer in patients suffering from multiple malignancies (n=90). **d** Anatomic distribution of tertiary cancer in patients suffering from multiple malignancies (n=15)

Diagnosis of secondary cancer	Patients n=75		
- clinical examination	4	20 simultaneous	panendoscopy 22
- during surgery	7		
- panendoscopy	9		
- clinical examination - CT - ultrasound	36 5 1	55 synchronous/ metachronous	
- panendoscopy	13		
patient himself, general physician, dentist	14		

Fig. 2 Diagnosis of secondary cancer in patients developing second primary tumours with regard to patients in continuous follow-up examinations (n=55) and use of panendoscopy (n=22)

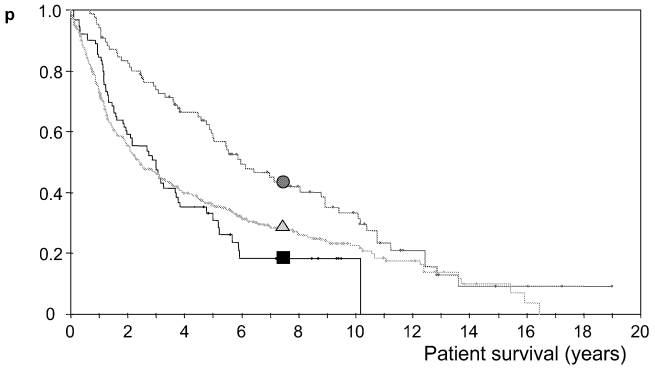
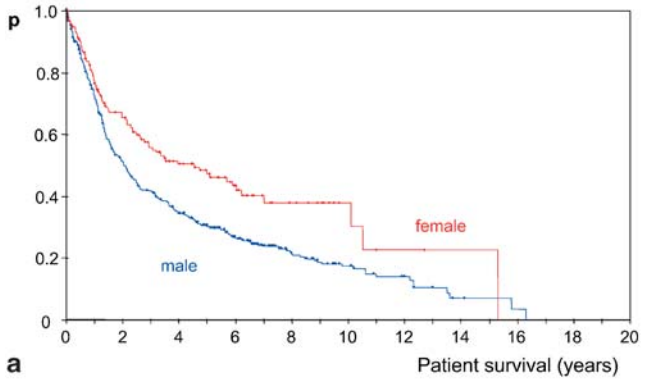
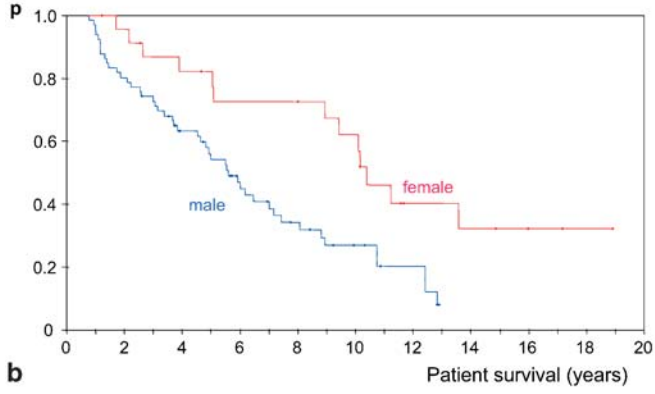


Fig. 3 Survival rate (Kaplan-Meier) of patients with oropharyngeal cancer after the diagnosis of the index or single carcinoma (*triangle*), second primary tumours after diagnosis of the index carcinoma (*grey circle*), second primary tumours after diagnosis of the secondary carcinoma (*black square*)

metastases and tumour recurrences were present. Of all examined patients, 440 died within the observation period; 84 patients (8.6%) died within the first 6 months after diagnosis of the index tumour and 164 patients (16.7%) within the first year. Only 15 patients died later than 10 years after the diagnosis. Of those patients who were alive, 112 patients were screened in follow-up examinations within the last year. The status of the remaining 429 patients (43.7%) was classified as uncertain. Related to all patients, the average interval between diagnosis of the single or index tumour and death of the patient was 2.4 years (Fig. 3). The prognosis of female patients was better than that of male patients (Fig. 4a).

Sixty of the 90 patients (66.7%) with second primary tumours died within the observation period. Of those 30 patients who were alive, 25 (27.8%) patients were screened in follow-up examinations within the last year of the study. The status of the remaining five patients (5.6%) was classified as uncertain. Related to all patients, the arithmetic average interval between diagnosis of the single or index tumour and death of the patient was 5.2 years. Female patients had a better prognosis than male patients (Figs. 3 and 4b).





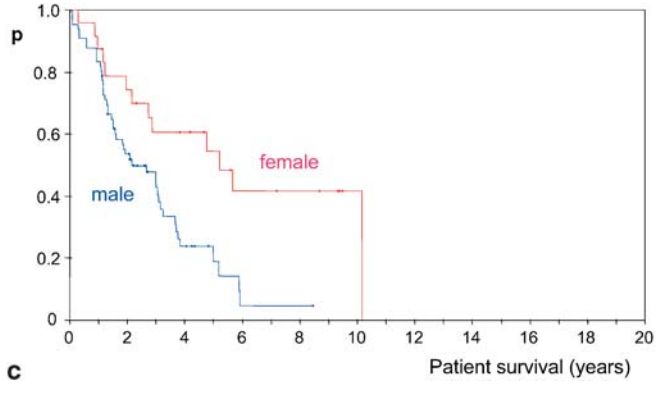


Fig. 4 **a** Gender distribution of survival rate (Kaplan-Meier) in patients with oropharyngeal after diagnosis of the single or index carcinoma. **b** Gender distribution of the survival rate (Kaplan-Meier) in patients with oropharyngeal cancer after diagnosis of the single or index carcinoma. **c** Gender distribution of survival rate (Kaplan-Meier) in patients with second primary tumours after diagnosis of the secondary carcinoma

Of the 60 patients (66.7%) with second primary tumours who died within the observation period, seven patients (7.8%) died within the first 6 months after diagnosis of the second malignancy and 14 patients (15.6%) within 1 year. Only one patient (1.1%) died after more than 10 years after diagnosis. Related to all patients, the arithmetic average interval between diagnosis of the second primary tumour and death of the patient was 2.3 years. Female patients exhibited a better prognosis than male patients (Figs. 3 and 4c). The interval between

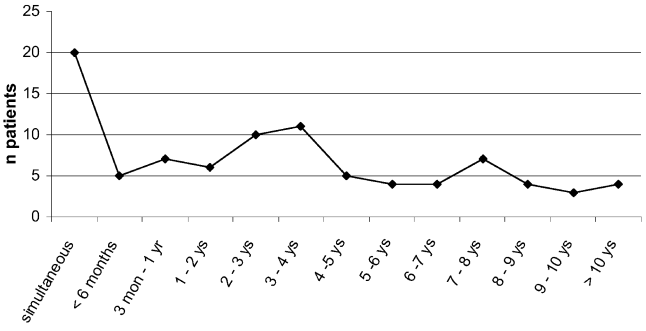


Fig. 5 Interval between diagnosis of index carcinoma and secondary carcinoma (n=90)

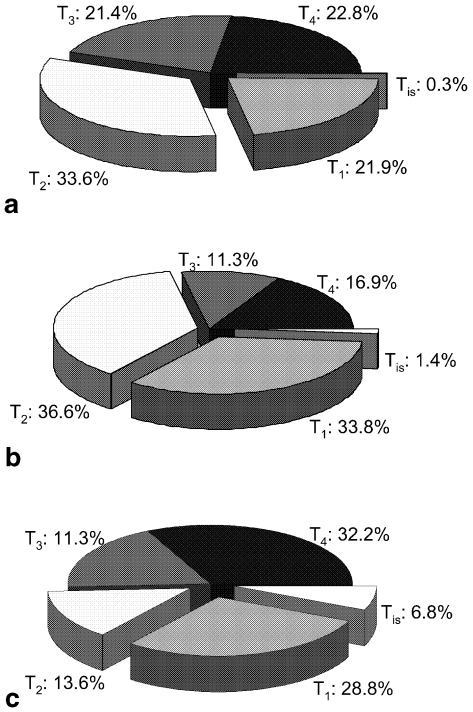


Fig. 6a–c Documented tumour sizes by T-stages: **a** T-stages of single or index tumour in all patients (n=780), **b** T-stages of index tumour in patients with second primary tumours (n=71), **c** T-stages of second or tertiary carcinoma (n=59)

the diagnosis of the index carcinoma and the diagnosis of an additional cancer extended 3.4 years on average. In 20 patients (22.2%) second or further primary tumours were diagnosed simultaneously, in 25 patients (27.8%) synchronously and in 65 patients (72.2%) metachronously (Fig. 5).

The size of the single or index tumour was assessed in 780 of the 981 patients (79.5%) in which TNM reports were available (Fig. 6a–c)

More than 50% of all examined patients (n=492) were treated by surgery alone; 208 patients were not treated or treatment was not documented sufficiently. The combination of surgery and chemotherapy/radiotherapy was applied to 149 patients (15.2%); other concepts such as

radiotherapy alone (1.2%), chemotherapy alone (0.7%) or immune therapy in combination with others (1.3%) were applied only rarely.

In patients with second primary tumours, initially 65 patients (72.2%) and in secondary cancer 31 patients (34.4%) were treated by surgery alone. Two index carcinomas (2.2%) and 20 secondary cancers (22.2%) were treated exclusively non-surgically. Twenty-three index carcinomas (25.6%) and 29 secondary cancers (32.2%) were treated both surgically and non-surgically. Consequently, the ratio of surgical to non-surgical treatment concepts was for the index carcinoma 3.52:1, for secondary cancer 1.22:1, and for tertiary cancer 1:1.

In the group of all patients, 440 patients died (44.9%) during the observation period. In the group of patients with second primary tumours, 60 patients died (66.7%); in 46 of them (76.7%) death was definitely caused by the tumour, in two patients (3.3%) likely caused by the tumour and in three patients (5%) not caused by the tumour. In nine patients, the reason of death is unknown.

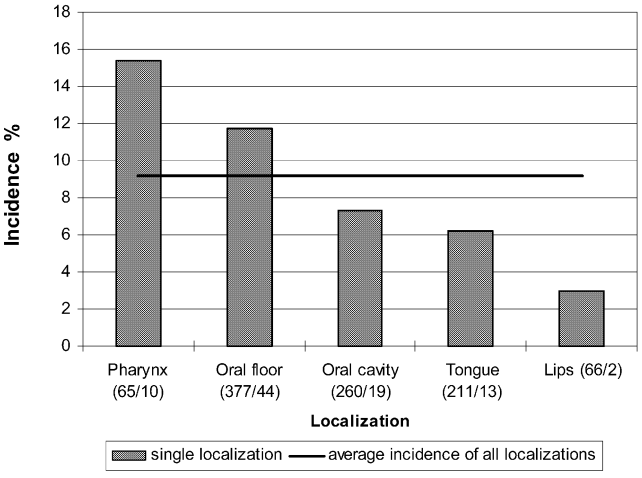


Fig. 7 Incidence of second primary tumours related to the anatomic localisation of the index tumour (n index tumours / n secondary carcinoma)

Discussion

The incidence of 9.2% of second primary tumours in patients with oropharyngeal carcinoma presented in this study seems comparable to published reports of similar patient populations with oropharyngeal tumours [15, 18, 21, 23]. The gender distribution exhibited an increasing number of female patients affected by oropharyngeal cancer, thus probably reflecting altered social roles of females in western societies [1, 11, 30]. The preferred localisation of the tumours at the oral floor seems somewhat unusual when compared with other studies. In the otorhinolaryngeal literature, the larynx and the oesophagus often have been reported as preferred tumour localisations [9, 23], while in the literature of oral and maxillofacial surgery the tongue, oral cavity and pharynx are found [14, 27]. The categorisation of anatomic localisations applied in this study is the same as in earlier reports [2, 3, 8, 14, 22]; and especially the studies of Licciardello et al. and Shaha et al. [14, 22] confirmed the oral floor as the predominant localisation of tumour genesis in oropharyngeal cancer. Until now, there exists no clear scientific explanation for the different incidences of second primary tumours related to the localisation of the index tumour, which are found in other reports as well [8, 9, 12]. Probably different levels of susceptibility to exogenous carcinogenic factors related to certain anatomic locations have to be considered; another explanation might include the time of exposure to certain cancerogenic factors, which might be different in distinct anatomical regions of the aerodigestive system.

In this study, nearly every second simultaneous (45%) and 20% of all metachronous second primary tumours were detected by panendoscopy. When compared with other diagnostic tools such as radiology [17] or cytology [14], the potential of panendoscopy is controversial regarding risk, costs and efficacy. Levine and Nielsen [13] reported that barium contrast radiography allowed correct diagnosis of only 90% of tumours of the aerodigestive system, excluding small tumours of less than 1 cm diameter. They concluded that tumours smaller than 1 cm in diameter could be diagnosed correctly only by panendoscopy. Vogl and Steger [29] described panendoscopy as the most important diagnostic tool in the diagnosis of tumours of the larynx and hypopharynx, while in the oral cavity and the oropharynx they recommended direct inspection combined with magnetic resonance tomography for the assessment of infiltrative depth. Similarly, Gluckmann et al. [4] suggested panendoscopy for the further diagnosis in each patient with carcinoma of the upper aerodigestive tract and McDonald et al. [19] recommended its application every 3–6 months for follow-up. Additionally, panendoscopy would be helpful in the diagnosis of other superficial alterations such as leukoplakia.

In general, in this study the additional malignancies were located more caudal and posterior than the index carcinoma (Fig. 7), which generally complicated their detection in follow-up examinations and probably required panendoscopy more often.

Survival after oropharyngeal carcinoma was enhanced in patients with second primary tumours. This somewhat surprising observation is consistent with the literature [5, 7, 12] and probably can be explained by patients with metachronic second primary tumours who survive a certain period before an additional malignancy is diagnosed. Those patients with severe index carcinomas die before a second malignancy occurs. The reduced survival of patients with second primary tumours probably results from a more difficult diagnosis and therapy of the additional cancer as a consequence of scar formation and irregular anatomy. In this study, the interval between the diagnosis of index tumour and second primary tumours extended 3.4 years on average and 4.7 years in patients with metachronous second primary tumours alone. Shik-

hani et al. [23] and Brandau and Glanz [2] reported only 1.4 and 1.7 years, but Panosetti et al. [20] and Lamprecht et al. [9] confirmed the results of this study with 4 and 4.5 years, respectively. The ratio of patients with metachronous to simultaneous and synchronic second primary tumours was 1:2.6 in this study. Most likely due to methodic differences of the studies, this ratio was reported to vary between 1:3 [24], 1:1[23], 1.5:1 [6] and 2:1 [32].

Index tumour sizes of T3/4 were found in 44.2% of all examined patients, but only in 28.2% of patients who developed second primary tumours. Probably many patients with T3/4 stages die before a second malignancy develops (Fig. 8a). In patients with multiple malignancies, T3/4 stages occurred frequently; one reason might be the preferred dorso-caudal position of these tumours, which were probably more difficult to diagnose. This is opposed by the fact that more than 62% of all second primary tumours were found in follow-up examinations; therefore, they should be found at earlier stages. Similar data were reported by Lyons [16], who found T3/4-stages in 36.8% of index carcinomas and in 50% of the second primary tumours. The increased tumour size was related to a reduced survival of the patients both after diagnosis of the index carcinoma (Fig. 8b) and more clearly after diagnosis of an additional cancer (Fig. 8c).

In this study, 50.2% of all patients were treated exclusively by surgery, and in 24.7% of all patients, surgery was combined with other procedures. This is similar to other reports [3, 8] and demonstrates the predominance of surgery in the therapy of oropharyngeal carcinoma. Of patients developing second primary tumours, 72.2% had been treated exclusively by surgery, and in 25.6% of these patients surgery had been combined with other procedures.

In those 90 patients with second primary tumours, only 34.4% were treated exclusively by surgery, and 32.2% by surgery and other procedures. Related to the presence and size of an additional malignancy treatment concepts were changed progressively from surgical to non-surgical procedures. Motives include the often bad conditions of the patients suffering from second primary tumours and the disability to reconstruct extended defects in the upper aerodigestive tract. Reasons of death in patients with second primary tumours were tumour related in 76.7% of patients. This is similar to reports of McDonald et al. [19].

In conclusion, this study demonstrates that second primary tumours have to be considered a frequent phenomenon in oropharyngeal cancer. Despite regular follow-up concepts, additional carcinomas are often detected at high T-stages, probably due to their preferred dorsoposterior localisation. Panendoscopy has proven to serve as a reliable diagnostic tool for the detection of second primary tumours. Once second primary tumours are diagnosed, treatment concepts have to be changed from surgical to non-surgical techniques. Most patients with second primary tumours die due to tumour-related causes within 4 years.

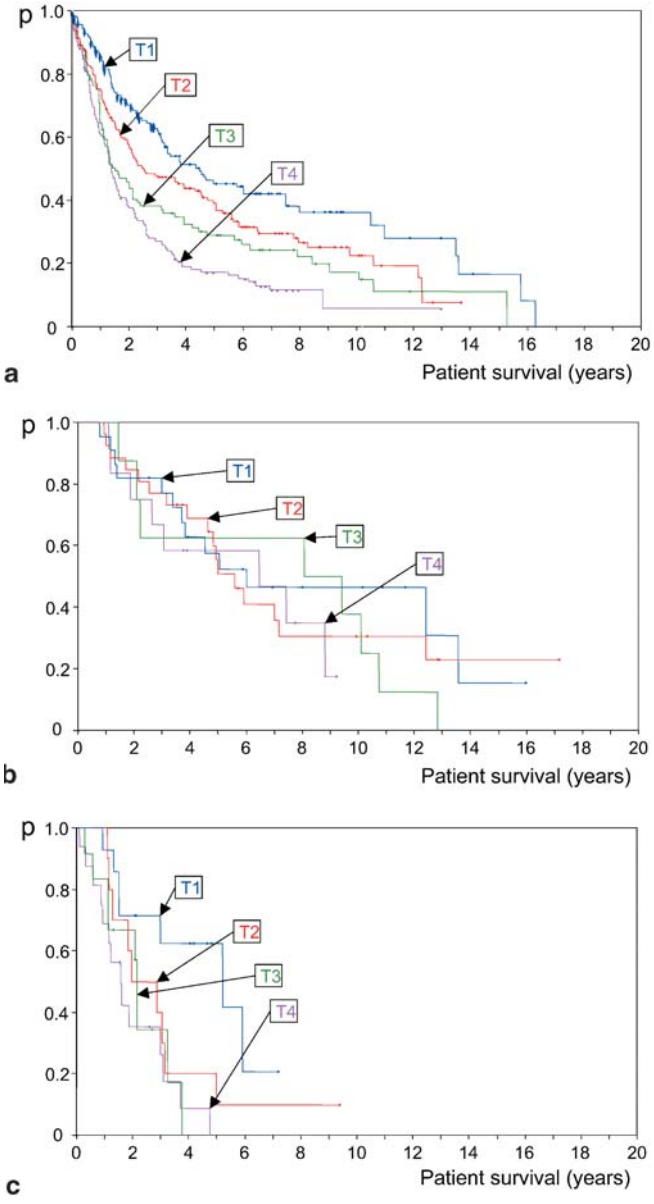


Fig. 8. a Survival of patients (Kaplan-Meier) with oropharyngeal cancer after diagnosis of the single or index carcinoma related to the T-stage of the carcinoma. **b** Survival of patients (Kaplan-Meier) with second primary tumours after diagnosis of the index carcinoma related to the T-stage of the carcinoma. **c** Survival of patients (Kaplan-Meier) with second primary tumours after diagnosis of the secondary carcinoma related to the T-stage of the secondary carcinoma

References

1. Boysen M, Loven JO (1993) Second malignant neoplasms in patients with head and neck squamous cell carcinomas. Acta Oncol 32:283–288
2. Brandau P, Glanz H (1989) Multicentric cancer spread in the mouth cavity and oropharynx. HNO 37:485–489
3. Eckardt A (1993) Clinical impact of synchronous and metachronous malignancies in patients with oral cancer. Int J Oral Maxillofac Surg 22:282–284

4. Gluckman JL, Crissman JD, Donegan JO (1980) Multicentric squamous-cell carcinoma of the upper aerodigestive tract. Head Neck Surg 3:90–96
5. Haughey BH, Arfken CL, Gates GA, Harvey J (1992) Meta-analysis of second malignant tumors in head and neck cancer: the case for an endoscopic screening protocol. Ann Otol Rhinol Laryngol 101:105–112
6. Healey GB, Strong MS, Uchmakli A (1978) Carcinoma of the palatine arch. The rationale of treatment selection. Am J Surg 132:498–503
7. Hemprich A, Breier T, Kovacs G (1992) Long-term results of radical therapy of squamous cell cancers of the mouth with special reference to late recurrence and second malignancies—a catamnestic study of 20 years. In: Schwenzer N (ed) Fortschritte der Kiefer-Gesichts-Chirurgie, vol. 37, Thieme, Stuttgart, New York, pp 43–45
8. Jovanovic A, van der Tol IG, Kostense PJ, Schulten EA, de Vries N, Snow GB, Van der Waal I (1994) Second respiratory and upper digestive tract cancer following oral squamous cell carcinoma. Oral Oncol Eur J Cancer 30:225–229
9. Lamprecht J, Lamprecht A, Morgenstern C (1983) Multiple tumors in the upper aerodigestive tract—a retrospective study. Laryngol Rhinol Otol 62:499–501
10. Larson J, Adams G, Abdel H (1990) Survival statistics for multiple primaries in head and neck cancer. Otolaryngol Head Neck Surg 103:14–24
11. Lefor AT, Bredenberg CE, Kellmann RM, Aust JC (1986) Multiple malignancies of the lung and head and neck. Arch Surg 121:265–270
12. Leon X, Ferlito A, Myer CM, Saffiotti U, Shaha A, Bradley PJ, Brandwein MS, Anniko M, Elluru RG, Rinaldo A (2002) Second primary tumours in head and neck cancer patients. Acta Otolaryngol 122:765–778
13. Levine B, Nielsen EW (1992) The justifications and controversies of panendoscopy—a review. Ear Nose Throat J 71:335–341
14. Licciardello JTW, Spitz M, Ki Hong W (1989) Multiple primary cancer in patients with cancer of the head and neck: second cancer of the head and neck, esophagus and lung. Int J Radiat Oncol Biol Phys 17:467–476
15. Lundgren J, Olofsson J (1986) Multiple primary malignancies in patients treated for laryngeal carcinoma. J Otolaryngol 15:145–150
16. Lyons MF, Redmond J, Covelli H (1986) Multiple primary neoplasia of the head and neck and lung. Cancer 57:2193–2197
17. Malefatto JP, Kasimis BS, Moran EM, Wuerker RB, Stein JJ (1984) The clinical significance of radiographically detected pulmonary neoplastic lesions in patients with head and neck cancer. J Clin Oncol 2:625–630
18. Masaki N, Hashimoto T, Ikeda H, Inoue T, Kozuka T (1987) Multiple primary malignancies in patients with head and neck cancer. Jpn J Clin Oncol 7:303–307
19. McDonald S, Haie C, Rubin P, Nelson D, Divers LD (1989) Second malignant tumors in patients with laryngeal carcinoma: diagnosis, treatment, and prevention. Int J Radiat Oncol Biol Phys 17:457–465
20. Panosetti E, Luboinski B, Mamelle G, Richard JM (1989) Multiple synchronous and metachronous cancers of the upper aerodigestive tract: a nine-year study. Laryngoscope 99:1267–1273
21. Panosetti E, Arnold W, Muller W (1990) Site and incidence of multiple cancers in patients with squamous cell carcinomas of the upper aerodigestive tract. Laryngol Rhinol Otol 69:449–453
22. Shaha AR, Hoover EL, Mitrani M, Marti JR, Krespi JP (1988) Synchronicity, multicentricity and metachronicity of head and neck cancer. Head Neck Surg 10:225–228
23. Shikani AH, Matanoski GM, Jones MM, Kashima HK, Johns ME (1986) Multiple primary malignancies in head and neck cancer. Arch Otolaryngol Head Neck Surg 112:1172–1179
24. Shons A, McQuarrie D (1985) Multiple primary epidermoid carcinomas of the upper aerodigestive tract. Arch Surg 120:1007–1009
25. Slaughter DP (1946) Multicentric origin of intraoral carcinoma. Surgery 20:133–134
26. Slaughter DP, Southwick HW, Smejkal W (1953) "Field cancerization" in oral stratified squamous cell epithelium. J Am Cancer Soc 6:963–968
27. Tachimori Y, Watanabe H, Kato H, Ebihara S, Ono I, Nakatsuka T, Harii K (1990) Treatment for synchronous and metachronous carcinomas of the head and neck and esophagus. J Surg Oncol 45:43–45
28. UICC (1997) TNM-Classification of malignant tumours. Springer, Berlin, Heidelberg, New York
29. Vogl TJ, Steger W (1996) Imaging of head and neck Tumours. Onkologe 2:328–338
30. de Vries N (1994) Second primary tumors in oral and oropharyngeal cancer. Recent Results Cancer Res 134:121–132
31. Warren S, Gates O (1932) Multiple primary malignant tumors: a survey of the literature and a statistical study. Am J Cancer 21:1358–1414
32. Weaver A, Fleming SM, Knechtges TC (1979) Triple endoscopy: a neglected essential in head and neck cancer. Surgery 86:493–496