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Survival benefit for patients treated in a certified head and neck tumor center

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Abstract. – OBJECTIVE: Increasing effort has been put in the implementation and certification of head and neck tumor centers in order to establish standardized, quality assured health care for head and neck tumor patients. This study evaluated survival rates after treatment in a certified head and neck tumor center (CHNTC) vs. a non-certified head and neck tumor center (non-CHNTC) in Middle Franconia, Germany.

PATIENTS AND METHODS: Age, sex, possible obituary, and typical relevant prognostic variables were analyzed. Diagnosis was recorded according to ICD10. Clinical and pathological TNM staging, tumor grading, localization, R-stage, and morphology were assessed (ICD-0). Patients diagnosed with oral cancer (N=1047) were divided into groups based on where they received their primary treatment; CHNTCs or non-CHNTCs.

RESULTS: Patients treated at CHNTCs had significantly higher survival rates vs. those treated at non-CHNTC (p=0.023) in univariate analysis. In a Cox regression model, survival rates for patients with pN0 and pN+ stage were similar at both types of centers. Men with pN0 had significantly lower survival rates (HR=0.497, p<0.001). Age had a statistically significant influence on survival rates independently from pN stage (HR=1.031 per year, p<0.001 in both groups).

CONCLUSIONS: Patients treated at CHNTC had better survival rates than those treated at non-CHNTC.

Key Words:
Head and Neck Tumor Center, Certification, Prognosis, Survival.

Introduction

Quality management, accreditation, and certification have received considerable attention in recent decades. The aim is usually to increase effectiveness and efficiency whilst generating flagships. According to Social Code V, §§ 135 and 136, service providers are obliged to ensure and further develop the quality of their services. Shaw showed that ISO 9001 certification has positive effects on patient safety, for example, but not on clinical practice[1]. QM processes are complex, time-consuming, and expensive, and the current data situation does not allow reliable conclusions for or against certification processes[2].

In 2003, the German Cancer Society (GCS) and oncological active societies joined forces to adapt existing structures of supply to the needs of modern cancer therapy[3]. The goal of the GCS is to promote the establishment of oncological centers, with a defined qualitative claim on a voluntary basis to improve the care of patients with cancer. In oncological centers, affected patients can be treated during all phases of the disease. Currently, there are 41 Certified Head and Neck Tumor Centers (CHNTCs) in Germany[4]. Certification follows a three-step approach, which is also part of the national cancer plan of the German Federal Health Ministry[5]. The national cancer plan regulates and supports cooperation and requests the creation and application of evidence-based guidelines, the quality assurance of

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treatment in certified centers, and the transparent acquisition and representation of the long-term results of treatment[6]. Survey sheets are the basis of certification.

The clinical practice guideline for oral cavity cancer is the mainstay for treatment[7]. Quality indicators were based on the guideline (Table I)[3]. First studies indicated a positive impact, but a comparison between certified and non-certified centers has not yet been done in the field of head and neck cancer[8]. A study by Beckmann et al[9] emphasizes the benefit derived from treatment at certified breast centers, but lacked several important variables in the regression analysis. Kreienberg et al[10] also confirmed improved treatment at certified centers.

Approximately 5% of all malignant tumors are limited to the oral cavity, and 95% correspond to Oral Squamous Cell Carcinoma (OSCC). OSCC accounts for 200,000 to 350,000 new cases each year. The 5-year survival rate is approximately 55% in Germany[11]. Metastasis occurs primarily in the cervical lymph nodes, followed by more distant lymph nodes and distant metastases, mainly lung metastases[12-14]. The primary treatment is the timely removal of the primary tumor, with a resection safety distance of 3-5 mm[15]. Tobacco and alcohol consumption are risk factors for development, metastases, and relapse[16]. Furthermore, the TNM classification provides other relevant parameters regarding prognosis. A higher T stage is associated with a poorer prognosis[17]. According to Massano et al[16] local metastasis in cervical lymph nodes is correlated with an increased relapse rate.

Studies have shown that tumor grade is an independent factor for distant metastases and, therefore, prognosis[18]. In addition to the maximum tumor extent, tumor thickness (<5 mm) seems to be directly linked with lymph node metastases[19]. Patients with regional lymph node metastasis and perineural infiltration are known to have an increased likelihood of distant metastases[20]. Shaw et al[21] described a connection between extracapsular tumor spread and lymph node metastases and a shortened survival. Furthermore, microvascular invasion is an independent prognostic factor in OSCC[22]. In addition, preoperative dental procedures, like extractions or incisions, can lead to metastases and distant metastasis[23]. Despite various treatment strategies, initial studies have so far not determined an improvement in outcomes[24].

The aim of this study was to evaluate survival rates after treatment at a CHNTC compared to treatment at non-certified tumor centers in Middle Franconia. Furthermore, survival rates were compared to the actual literature.

Patients and Methods

Patient Selection and Grouping

Registration in the clinical cancer registry is based on state law. Patients have the right to deny or revoke registration at any time.

Patients living in Middle Franconia who reported to our clinical cancer registry between 2000 and 2012 were included in this study. Included diagnoses were malignant neoplasm of other and unspecified parts of the tongue (C02), malignant neoplasm of the gum (C03), malignant neoplasm of the floor of the mouth (C04), oral cancer of the palate (C05), malignant neoplasm of other and unspecified parts of the mouth (C06), malignant neoplasm of the parotid gland (C07), and malignant neoplasm of the accessory sinuses (C31).

Follow Up

Follow up time ranged from 0 to 194.1 (mean=56.84, standard deviation [SD]=46.95) months. Patients with primary palliative treatment and or neoadjuvant treatment were excluded as well as incomplete follow up data concerning analyzed variables.

Two groups were created. CHNTC-group consisted of patients who received their primary

Table I. Cox regression models. Significant covariates (except group) within the Cox model are in bold. CHNTC = cancer of the head and neck treatment centers; HR = hazard ratio.

	HR	95% CI	p
Group (reference: CHTCNC)	1.147	0.957 - 1.373	0.137
Sex (reference: M)	0.644	0.523 - 0.793	<0.001
Age	1.030	1.022 - 1.039	<0.001
pN (reference: pN0)	2.140	1.785 - 2.566	<0.001

treatment at the CHNTC. Non-CHNTC-group consisted of patients who received their primary treatment outside the CHNTC.

Variables

Besides age, sex, and a possible obituary, typical relevant prognostic variables were analyzed. Diagnosis was recorded according to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD10). Clinical and pathological TNM staging was performed as well as tumor grading, tumor localization, R-stage, and morphology.

Statistical Analysis

Descriptive statistics were carried out for every variable. In addition, Kaplan-Meier estimator and log-rank tests were performed for every categorical factor.

Afterwards, Cox regression was used to identify possible covariates. Hazard ratios (HR) and p values were calculated and interpreted. A $p < 0.05$ was regarded as statistically significant. Calculations were carried out using R V3.3.2 (R Core Team [2016], where R is a language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 1047 patients were included in this study. Patients' mean age was 60.7 (±12.3) years; 478 (45.65%) patients were treated at CHNTCs and 569 (54.34%) patients were treated at non-CHNTCs.

Univariate Analysis

Women (n = 330) had a statistically significant, better survival rate than men (n = 717, $p<0.001$). Patients with parotid tumors had statistically significant ($p<0.001$), better survival rates than those with malignant neoplasms of the gum. The 5-year survival of patients with pT1 tumors was 0.692 *vs.* 0.404 for patients with pT4 tumors (log-rank test: $p<0.001$). Those with pN0 tumors had statistically significant, better survival compared to patients with pN+ ($p<0.001$). The higher the tumor grade or R-stage, the lower the survival rate ($p<0.001$). Morphology showed no statistically significant influence on survival rates.

Patients treated at CHNTCs had a statistically significant, higher survival rate (Figure 1) compared to patients treated outside CHNTCs ($p=0.023$).

Multivariate Analysis

To analyze covariates, a Cox regression model was performed using the variables group, age, sex, pT, pN, grading, and R-stage as independent variables. pT, grading, and R-stage showed no significant influence and were dropped from the analysis. The CHNTC-group, which also showed no significant influence in all the models, was further considered because it was of major interest in this study. The HRs and p-values of all variables are shown in Table II. Although the CHNTC-group showed a significant difference in survival in the univariate analysis, the influence was no longer significant when pN was considered. To examine the interaction between pN and group with high interpretability of HRs, Cox models for pN0 patients and pN+ patients were calculated separately as shown in Table III. Within the pN0 and the pN+ group, the survival rates between groups were almost the same. Furthermore, men with pN0 stage tumors had a statistically significant, lower survival rate (HR=0.497, $p<0.001$), whereas this difference disappeared in men with pN+ stage tumors. Age had a statistically significant influence on survival rates independently from pN stage (HR=1.031 per year, $p<0.001$ in both groups).

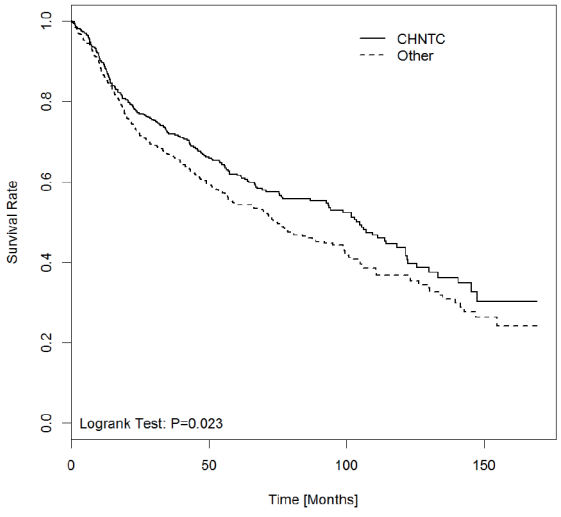

Figure 1. Comparison of survival curves between patients treated at a CHNTC *vs.* those treated outside a CHNTC (5-year survival: 0.614 [CHNTC] *vs.* 0.546 [other]; $p=0.017$).

Discussion

Middle Franconia has about 1.7 million inhabitants. Therefore, this study covers about 2% of the German population within a time frame of 11 years. Many head and neck tumor studies are derived from large experienced tumor centers. Nonetheless, none of these tumor centers have yet compared themselves to other centers. This study aimed to analyze prognosis and relevant prognostic factors in a CHNTC compared to non-certified HNTCs. Certification is a time-consuming and expensive process. Despite that, an evidence-based benefit has not yet been demonstrated. As mentioned above, a study from 2011 showed a survival benefit in patients with breast cancer who were treated at certified breast cancer centers[9]. The study included 3940 patients and showed better survival for patients treated at these centers independent of known prognostic factors, diagnosis, and treatment compared to other centers. Possible reasons discussed were a Hawthorne-like effect and differences in survival measurement. Furthermore, several important prognostic variables were missing in the statistical model. Four years later, a similar multicenter study including 32,789 patients showed no survival benefit for patients with breast cancer in general, although elderly patients had a survival benefit[25]. The authors hypothesized that this benefit may be caused by comorbidities. Therefore, comorbidities, and maybe even a health status score, should be better represented in tumor databases. Three years after to the last study, another study by Kreienberger et al(10), including 8323 patients, found several benefits including overall survival.

In our study, age was a relevant prognostic factor. Age showed statistically significant results in all Cox models and, consequently, seems to be an independent risk factor. European guidelines do not regard age as a prognostic factor, but correlated age with the incidence of comorbidities[26]. In contrast, American guidelines recognize age as a prognostic factor[27]. Our study suggests that age is a relevant prognostic factor for patients who have head and neck cancer. Yet, the risk of surgery and anesthesia is very often the only curative solution. Nonetheless, this data indicates that whether following European or American guidelines, elderly patients, relatives, and physicians should be aware of this inescapable risk factor.

Gender was a risk factor in the Cox model in the pN0 group, but not in the pN+ group. Within industrialized countries, women live about five to ten years longer than men for various reasons. For decades, female smokers were scarcer then male ones. As smoking has become more prevalent in women, this effect might be temporary[28]. Interestingly enough, gender showed no significance in the pN+ group. This raises the question as to whether a positive pN+ status determines the prognosis, independent from covariates.

When looking at the variable "group" – and seeing no significant difference – the first question that arises is that one group may be treating more advanced tumors. We analyzed the groups and found no difference between the populations. All staging and grading parameters were distributed equally.

This point makes a fact unmistakably clear; despite improved procedures, an interdisciplinary team, and many other instruments, it does not currently matter where a patient with a head and neck tumor undergoes surgery. It is not a satisfactory fact, but it is a motivating one because the cause may be found in tumor biology and further research is necessary. It raises the question as to whether tumor mechanisms exist that lead to a "point of no return". For this reason, it would be desirable to answer the fundamental questions about head and neck tumors. Another point is hidden in the postoperative therapy regimens.

Table II. pN stage-dependent Cox model. Significant covariates (except group) within the pN stage-dependent Cox model are in bold. CHNTC = cancer of the head and neck treatment centers; HR = hazard ratio.

		HR	95% CI	*p*
pN0	Group (reference: CHTCNC)	1.224	0.964 - 1.553	0.098
	Sex (reference: M)	0.497	0.374 - 0.661	<0.001
	Age	1.031	1.02 - 1.041	<0.001
		HR	95% CI	*p*
pN+	Group (reference: CHTCNC)	1.036	0.786 - 1.364	0.803
	Sex (reference: M)	0.906	0.667 - 1.229	0.524
	Age	1.028	1.016 - 1.041	<0.001

Table III. Patient characteristics. CHNTC = cancer of the head and neck treatment centers; NA = not assessed; SD = standard deviation.

	All patients	CHNTC	Other	p
N	1047	478	569	
Mean age, years (SD)	60.7 (12.3)	60.3 (12.1)	61 (12.6)	0.538
Gender, n (%)				1
Female	330 (31.5)	151 (31.6)	179 (31.5)	
Male	717 (68.5)	327 (68.4)	390 (68.5)	
pT, n (%)				0.96
pT1	490 (46.8)	223 (46.7)	267 (46.9)	
pT2	277 (26.5)	130 (27.2)	147 (25.8)	
pT3	114 (10.9)	51 (10.7)	63 (11.1)	
pT4	166 (15.9)	74 (15.5)	92 (16.2)	
pN, n (%)				0.031
pN0	708 (67.6)	340 (71.1)	368 (64.7)	
pN+	339 (32.4)	138 (28.9)	201 (35.3)	
Grading, n (%)				0.054
1	200 (19.1)	92 (19.2)	108 (19)	
2	523 (50)	255 (53.3)	268 (47.1)	
3	275 (26.3)	107 (22.4)	168 (29.5)	
4	7 (0.7)	4 (0.8)	3 (0.5)	
NA	42 (4)	20 (4.2)	22 (3.9)	

Especially in radiation therapy, there are many different protocols and modalities, and clear statements about which protocol is the most favorable do not yet exist[29].

Nonetheless, there is a statistically significant, survival benefit for patients treated at a CHNTC. There are multiple possible explanations for this benefit, but in the end they are vague. Nevertheless, this shows that certification creates an enormous advantage for patients. Patients should, therefore, be recommended for treatment at certified centers. In addition to the survival benefit, research could be supported by the concentration of cases. However, the breast centers have also shown that a certified center alone is not sufficient, but that study data from numerous centers have to be combined in order to obtain more meaningful data.

Conclusions

CHNTCs provided patients with better survival rates compared to non-CHNTCs. Various factors influence disease progression and prognosis. Patients should therefore be recommended to receive treatment at certified centers. In addition to the survival benefit, research could be supported by the concentration of cases. Furthermore, comorbidities, and maybe even health status scores, should be better recorded in tumor databases.

Conflict of Interest

The Authors declare that they have no conflict of interest.

References

1) Shaw CD, Groene O, Botje D, Sunol R, Kutryba B, Klazinga N, Bruneau C, Hammer A, Wang A, Arah OA, Wagner C, on behalf of the DPC, Klazinga N, Kringos DS, Lombarts K, Plochg T, Lopez MA, Secanell M, Sunol R, Vallejo P, Bartels P, Kristensen S, Michel P, Saillour-Glenisson F, Vlcek F, Car M, Jones S, Klaus E, Garel P, Hanslik K, Saluvan M, Bruneau C, Depaigne-Loth A, Shaw C, Hammer A, Ommen O, Pfaff H, Groene O, Botje D, Wagner C, Kutaj-Wasikowska H, Kutryba B, Escoval A, Franca M, Almeman F, Kus H, Ozturk K, Mannion R, Arah OA, Chow A, Der-Sarkissian M, Thompson C, Wang A, Thompson A. The effect of certification and accreditation on quality management in 4 clinical services in 73 European hospitals. IJQHC 2014; 26: 100-107.

2) Wagner C, Groene O, Thompson CA, Klazinga NS, Dersarkissian M, Arah OA, Suñol R, on behalf of the DPC, Klazinga N, Kringos DS, Lombarts M, Plochg T, Lopez MA, Secanell M, Sunol R, Vallejo P, Bartels P, Kristensen S, Michel P, Saillour-Glenisson F, Vlcek F, Car M, Jones S, Klaus E, Bottaro S, Garel P, Saluvan M, Bruneau C, Depaigne-Loth A, Shaw C, Hammer A, Ommen O, Pfaff H, Groene O, Botje D, Wagner C, Kutaj-Wasikowska H, Kutryba B, Escoval A, Lívio A, Eiras M, Franca M, Leite I, Almeman F, Kus H, Ozturk K, Mannion R, Arah OA, Chow A, DerSarkissian M, Thompson CA, Wang A, Thompson A. Development

and validation of an index to assess hospital quality management systems. IJQHC 2014; 26:16-26.

3) Winter A, Iro H, Wolff KD, Wesselmann S. Zertifizierung von Kopf-Hals-Tumor-Zentren durch die Deutsche Krebsgesellschaft. HNO 2013; 61: 914-920.

4) Onkozert GmbH. www.oncomap.de. 2017, Accessed: 05.04.2017.

5) Beckmann MW, Adler G, Albers P, Bruns J, Ehninger G, Hauschild A, Neuhaus P, Schmiegel W, Schmitz S, Schmoll H-J, Weller M, Wiegel T, Bamberg M. Onkologie dreistufenmodell optimiert behandlung unter kostendeckung wie die künftigen strukturen der onkologischen versorgung in Deutschland aussehen sollten. Dtsch Arztebl Int 2007; 104: 3004.

6) Bundesregierung Gd. Entwurf eines Gesetzes zur Weiterentwicklung der Krebsfrüherkennung und zur Qualitätssicherung durch klinische Krebsregister (Krebsfrüherkennungs und -registergesetz – KFRG). http://dipbt.bundestag.de/doc/btd/17/112/1711267.pdf 2012; Accessed: 05.04.2017.

7) Wolff KD, Follmann M, Nast A. The diagnosis and treatment of oral cavity cancer. Dtsch Arztebl Int 2012; 109: 829-835.

8) Wolff KD, Rau A, Ferencz J, Langer T, Kesting M, Nieberler M, Wesselmann S. Effect of an evidence-based guideline on the treatment of maxillofacial cancer: a prospective analysis. J Cranio Maxill Surg 2017; 45: 427-431.

9) Beckmann MW, Brucker C, Hanf V, Rauh C, Bani MR, Knob S, Petsch S, Schick S, Fasching PA, Hartmann A, Lux MP, Haberle L. Quality assured health care in certified breast centers and improvement of the prognosis of breast cancer patients. Onkologie 2011; 34: 362-367.

10) Kreienberg R, Wockel A, Wischnewsky M. Highly significant improvement in guideline adherence, relapse-free and overall survival in breast cancer patients when treated at certified breast cancer centres: an evaluation of 8323 patients. Breast 2018 ; 40: 54-59.

11) Listl S JL, Stenzinger A, Freier K, Emrich K. Survival of patients with oral cavity cancer in Germany. PLoS One 2013; 8: e53415.

12) Jones AS, Morar P, Phillips DE, Field JK, Husband D, Helliwell TR. Second primary tumors in patients with head and neck squamous cell carcinoma. Cancer 1995; 75: 1343-1353.

13) Shingaki S, Suzuki I, Kobayashi T, Nakajima T. Predicting factors for distant metastases in head and neck carcinomas: an analysis of 103 patients with locoregional control. J Cranio Maxillofac Surg 1996; 54: 853-857.

14) Wurm MC, Nkenke E, Neukam FW, Most T, Lutz R, Wehrhan F, Brunner K, Mitsimponas KT, Schlechtweg P, von Wilmowsky C. Case report: upper arm metastasis of an oral squamous cell carcinoma. BMC Oral Health 2015; 15: 22.

15) Sutton DN, Brown JS, Rogers SN, Vaughan ED, Woolgar JA. The prognostic implications of the surgical margin in oral squamous cell carcinoma. Int J Oral Maxillofac Surg 2003; 32: 30-34.

16) Massano J, Regateiro FS, Januario G, Ferreira A. Oral squamous cell carcinoma: review of prognostic and predictive factors. Oral Surg Oral Med Oral Pathol Oral Radiol 2006; 102: 67-76.

17) Eckert AW, Lautner MHW, Dempf R, Schubert J, Bilkenroth U. Prognostic factors for oral squamous cell carcinoma. Chirurg 2009; 80: 138-143.

18) Fortin A, Couture C, Doucet R, Albert M, Allard J, Tetu B. Does histologic grade have a role in the management of head and neck cancers? J Clin Oncol 2001; 19: 4107-4116.

19) P Oc, Pillai G, Patel S, Fisher C, Archer D, Eccles S, Rhys-Evans P. Tumour thickness predicts cervical nodal metastases and survival in early oral tongue cancer. Oral Oncol 2003; 39: 386-390.

20) Tarsitano A, Tardio ML, Marchetti C. Impact of perineural invasion as independent prognostic factor for local and regional failure in oral squamous cell carcinoma. Oral Surg Oral Med Oral Pathol Oral Radiol 2015; 119: 221-228.

21) Shaw RJ, Lowe D, Woolgar JA, Brown JS, Vaughan ED, Evans C, Lewis-Jones H, Hanlon R, Hall GL, Rogers SN. Extracapsular spread in oral squamous cell carcinoma. Head Neck 2010; 32: 714-722.

22) Grimm M. Prognostic value of clinicopathological parameters and outcome in 484 patients with oral squamous cell carcinoma: microvascular invasion (V+) is an independent prognostic factor for OSCC. Clin Transl Oncol 2012; 14: 870-880.

23) Takahashi H, Umeda M, Takahashi Y, Matsui T, Shigeta T, Minamikawa T, Shibuya Y, Komori T. Influence of preoperative dental procedures on the prognosis of patients with squamous cell carcinoma of the gingiva. Br J Oral Maxillofac Surg 2013; 51: 108-112.

24) Guntinas-Lichius O, Wendt T, Buentzel J, Esser D, Lochner P, Mueller A, Schultze-Mosgau S, Altendorf-Hofmann A. Head and neck cancer in Germany: a site-specific analysis of survival of the Thuringian cancer registration database. J Cancer Res Clin Oncol 2010; 136: 55-63.

25) Schrodi S, Tillack A, Niedostatek A, Werner C, Schubert-Fritschle G, Engel J. No survival benefit for patients with treatment in certified breast centers-a population-based evaluation of German Cancer Registry Data. Breast J 2015; 21: 490-500.

26) Kristensen SD, Knuuti J, Saraste A, Anker S, Botker HE, Hert SD, Ford I, Gonzalez-Juanatey JR, Gorenek B, Heyndrickx GR, Hoeft A, Huber K, Iung B, Kjeldsen KP, Longrois D, Luscher TF, Pierard L, Pocock S, Price S, Roffi M, Sirnes PA, Sousa-Uva M, Voudris V, Funck-Brentano C. 2014 ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management: The Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). Eur Heart J 2014; 35: 2383-2431.

27) Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B, Davila-Roman VG, Gerhard-Herman MD, Holly TA, Kane GC, Marine

JE, Nelson MT, Spencer CC, Thompson A, Ting HH, Uretsky BF, Wijeysundera DN. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. Developed in collaboration with the American College of Surgeons, American Society of Anesthesiologists, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Anesthesiologists, and Society of Vascular Medicine Endorsed by the Society of Hospital Medicine. J Nucl Cardiol 2015; 22: 162-215.

28) Lampert T, von der Lippe E, Müters S. Verbreitung des Rauchens in der Erwachsenenbevölkerung in Deutschland. Bundesgesundheitsblatt - Gesundheitsforschung - Gesundheitsschutz 2013; 56: 802-808.

29) De Felice F, Polimeni A, Valentini V, Brugnoletti O, Cassoni A, Greco A, de Vincentiis M, Tombolini V. Radiotherapy controversies and prospective in head and neck cancer: a literature-based critical review. Neoplasia 2018; 20: 227-232.