Oral Oncology 50 (2014) 651–656

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

25 Year survival outcomes for squamous cell carcinomas of the head and neck: Population-based outcomes from a Canadian province

M.S. Tiwana [a], J. Wu [b], J. Hay [b], F. Wong [c], W. Cheung [d], R.A. Olson [a,*]

[a] Radiation Oncology, BC Cancer Agency, Centre for the North, Prince George, British Columbia, Canada
[b] Radiation Oncology, BC Cancer Agency, Vancouver, British Columbia, Canada
[c] Radiation Oncology, BC Cancer Agency, Surrey, British Columbia, Canada
[d] Medical Oncology, BC Cancer Agency, Vancouver, British Columbia, Canada

ARTICLE INFO

Article history:
Received 17 October 2013
Received in revised form 17 February 2014
Accepted 23 March 2014
Available online 14 April 2014

Keywords:
Head and neck cancer
Population oncology
Overall survival
Head and neck cancer specific survival
Retrospective study

SUMMARY

Objectives: Long term outcomes of patients with head and neck cancer (HNC) are rarely reported, but of potential benefit to clinicians and researchers. Squamous cell carcinomas (SCC) of the head and neck represent a heterogeneous group of cancers. The purpose of this population based study is to describe primary site specific, long term outcomes of HNC.
Methods: All patients from a Canadian province diagnosed between 1986 and 1990 with SCC of the oral cavity, pharynx, and larynx were identified. Chart review and patient data were abstracted through the provincial cancer registry database. Survival analysis was performed with Kaplan Meier methods, while differences in survival between groups were assessed with log-rank tests. Multivariable analysis was performed using Cox-regression.
Results: 1657 patients were analyzed during the study period. Almost half (50.9%) of the cases were advanced stage (stage III IV) at presentation. Two, 5, 15 & 25 year overall survival (OS) and HNC specific survival for all the patients were 64%, 46%, 21%, 11% and 74%, 63%, 53% & 49%, respectively. OS and HNC-specific mortality were statistically inferior among men, older age at diagnosis, advanced stages of disease, and was primary cancer site specific, with worse survival in oropharyngeal & hypopharyngeal sites, $p < 0.001$.
Conclusions: Survival rates vary by primary HNC site, and the overall survival & HNC specific survival differ over this long follow up assessment. Head and neck cancer specific death is most common in the first five years, and is subsequently dominated by competing causes of mortality. These results are useful as a reference tool for clinicians, researchers, and trainees.

Introduction

Head and neck cancers (HNC) include cancers of the upper aerodigestive tract with the majority comprising the oral cavity, nasopharynx, oropharynx, hypopharynx, and larynx, with squamous cell carcinoma being the most common histopathology [1]. Annually, there is an incidence of approximately 550,000 new cases and 300,000 deaths due to HNC worldwide. The Cancer Surveillance & Outcomes division of BC cancer registry reports annual incidence of HNC to be 2.8% of all the cancers in the year 2010 [2]. Overall, the 5 year survival rates of HNC are around 50–60% [3].

The optimal treatment plan for HNC patients is often guided by survival outcome data. The reported outcomes of HNC in the literature are either from diverse populations or individual hospital based studies [4]. There are few databases like the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (NCI) which collects cancer survival and incidence information from population-based cancer registries [5]. However, SEER has its own set of inherent limitations, in particular selection bias and variation in data reporting. Historically, 5–10 year survival outcomes have been the choice of researchers to compare the efficacy and potential of ever increasing therapeutic options, and to understand the natural disease course. There is a paucity of scientific literature discussing long term HNC for the different primary sites, and cancer cohorts which are representative of a defined population.

* Corresponding author. Address: Radiation Oncology, BC Cancer Agency, Centre for the North, Prince George, British Columbia V2M 7E9, Canada. Tel.: +1 250 645 7300x687489; fax: +1 250 645 7361.
E-mail address: rolson2@bccancer.bc.ca (R.A. Olson).

http://dx.doi.org/10.1016/j.oraloncology.2014.03.009
1368-8375/

The primary aim of this retrospective study was to analyze the long term outcomes from a defined population residing within the province of BC. The BC Cancer Agency registry maintains the records of the population living in the BC's vast geography. The secondary objectives were to identify any differences between overall survival and head-and-neck cancer specific mortality, and to explore associations between patient and tumour characteristics with survival.

Materials and methods

The study was approved by the combined Research Ethics Board of the University of British Columbia & BC Cancer Agency. Chart review and patient data were abstracted through the BC cancer registry database. All patients with a head and neck squamous cell carcinoma (HNC) diagnosed from a five year period between 1986 and 1990 were included, as described below. The BC Cancer Agency is an agency of the Provincial Health Services Authority, provides a province-wide, population-based cancer control program for the residents of BC, Canada. The BC Cancer Agency is authorized through the BC Health Act and the BC Cancer Agency Research Information Regulation to operate the Cancer Registry for cancer surveillance and research.

Importantly, the BC Cancer Agency is the sole provider of radiotherapy in BC, and receives all pathologic diagnoses of cancer provincially.

Inclusion criteria

The inclusion criteria of the population in the study were: age $\geqslant$ 18 years, consecutive primary HNC patients diagnosed from January 1986 to December 1990, and histologically proven squamous cell carcinoma. Patients with a prior history of HNC and lesser frequent cancers of lip, paranasal sinuses, major salivary glands, or an unknown primary, were excluded from the analysis. Patients were staged according to the AJCC 5th edition classification for HNC [6].

Classification

Patients were classified by primary tumour site as follows: (1) oral cavity, (2) oropharynx, (3) glottic larynx, (4) non-glottic larynx, (5) nasopharynx, and (6) hypopharynx. Due to the relative different natural history, treatment approach, and survival outcomes within the subdivisions of HNC of larynx, laryngeal tumours were classified as "glottis" and "non-glottic" cancers. Survival data were available up to September 2011, amounting to 25 years of longitudinal assessment from the date of initiation of this study.

Survival data comparison

To comparatively validate our treatment outcomes with a standardized population based cancer research program, we utilized 2 & 5-year overall survival rates using the head and neck cancer

Table 1
Clinical & Treatment outcome characteristics.

Patient characteristic		Entire cohort, *N* = 1657 (100%)	Oral cavity *N* = 504 (30%)	Glottic larynx *N* = 334 (20%)	Non-glottic larynx *N* = 213 (14%)	Nasopharynx *N* = 131 (8%)	Oropharynx *N* = 348 (21%)	Hypopharynx *N* = 127 (7%)
Median Age [range], *y*		63 (18–103)	63.5 (18–103)	64.5 (34–93)	65 (34–91)	50 (21–91)	64 (26–91)	63 (37–88)
Proportion male		1233 (74%)	315 (62%)	302 (90%)	168 (79%)	94 (72%)	246 (71%)	108 (85%)
	0	2 (0.1%)	1 (0.2%)	1 (0.3%)	0	0	0	0
	1	301 (17%)	99 (20%)	142 (42.7%)	19 (8.9%)	3 (2%)	28 (9%)	10 (7%)
AJCC	2	352 (22%)	103 (20%)	120 (36%)	41 (19.2%)	15 (11%)	65 (19%)	8 (6%)
Staging 5th ed.	3	379 (23%)	92 (18%)	40 (12%)	49 (23%)	34 (26%)	121 (35%)	43 (34%)
	4A	327 (20%)	98 (19%)	11 (3%)	71 (33.3%)	50 (38%)	62 (17%)	35 (28%)
	4B	122 (7%)	15 (4%)	0	14 (6.6%)	18 (13)	51 (14%)	24 (20%)
	4C	13 (0.9%)	4 (0.8%)	0	1 (0.5%)	2 (1%)	2 (1%)	4 (3%)
	Unknown	161 (10%)	92 (18%)	20 (6%)	18 (8.4%)	18 (9%)	19 (5%)	3 (2%)
Treatment	Radiotherapy	1439 (87%)	378 (75%)	309 (93%)	182 (85%)	126 (96%)	324 (93%)	120 (95)
	Surgery	497 (30%)	237 (47%)	83 (25%)	61 (28%)	14 (11%)	73 (21%)	29 (23%)
	Chemotherapy	33 (2%)	6 (1%)	0	5 (2%)	2 (1.5%)	17 (5%)	3 (3%)

Table 2
2-year, 5-year, 15-year, & 25-year OS and HNC specific survival.

	Overall survival (OS)						HN Cancer Specific Survival (HNCSS)					
	Median OS ± SE years, 95% CI	Died of all causes	2 year (%)	5 year (%)	15 year (%)	25 year (%)	Median HNCSS ± SE years, 95% CI	HNC related deaths	2 year (%)	5 year (%)	15 year (%)	25 year (%)
Glottic larynx	8.72 ± 0.65(7.44, 9.99)	274 (82%)	83	67	32	16	Not reached	56 (17%)	92	86	81	75
Oral cavity	4.52 ± 0.65 (3.24, 5.78)	438 (87%)	65	49	23	12	Not reached	183 (36%)	76	68	57	51
Nasopharynx	3.41 ± 0.74 (1.97, 4.86)	103 (79%)	70	44	32	19	7.94 ± 4.81 (0, 17.36)	68 (52%)	75%	56	46	40
Non-glottic larynx	3.64 ± 0.54(2.59, 4.68)	199 (93%)	63	41	11	7	12.69 ± 3.93 (4.96, 20.37)	93 (44%)	72	58	46	43
Oropharynx	2.25 ± 0.25 (1.75, 2.75)	318 (91%)	54	36	14	7	4.41 ± 1.04 (2.37, 6.45)	186 (53%)	63	49	36	33
Hypopharynx	1.39 ± 0.13 (1.09, 1.58)	120 (94%)	34	14	8	4	1.49 ± 0.20 (1.09, 1.89)	84 (66%)	43	23	23	23

OS, overall survival; HNC, head-and-neck cancer.

Table 3
Multivariate Cox regression analysis.

Variables	Overall survival		HNC specific survival	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age (continuous yearly)	1.04 (1.04–1.05)	<0.001	1.02 (1.02–1.03)	<0.001
Female (versus male)	0.75 (0.69–0.88)	<0.001	0.91 (0.75–1.10)	0.34
Subsites				
Glottic larynx	1 (Reference)		1 (Reference)	
Oral cavity	1.43 (1.19–1.71)	<0.001	2.04 (1.45–2.88)	<0.001
Nasopharynx	1.13 (0.86–1.48)	0.37	1.99 (1.30–3.05)	0.01
Non-glottic larynx	1.30 (1.05–1.61)	0.02	1.71 (1.16–2.52)	0.01
Oropharynx	1.60 (1.32–1.94)	<0.001	2.57 (1.81–3.67)	<0.001
Hypopharynx	1.91 (1.48–2.45)	<0.001	3.46 (2.32–5.15)	<0.001
Stage				
I	1 (Reference)		1 (Reference)	
II	1.24 (1.03–1.49)	0.02	1.57 (1.04–1.89)	0.02
III	1.69 (1.43–2.05)	<0.001	3.30 (2.32–4.68)	<0.001
IV A	2.41 (1.97–2.93)	<0.001	4.95 (3.47–7.07)	<0.001
IV B	3.46 (2.66–4.50)	<0.001	7.66 (5.12–11.45)	<0.001
IV C	7.23 (3.74–13.97)	<0.001	12.7 (5.56–29.02)	<0.001
Treatment				
Surgery (versus not)	0.94 (0.72–1.25)	0.39	1.01 (0.82–1.23)	0.95
Radiation therapy (versus not)	1.12 (0.88–1.43)	0.35	1.31 (0.86–1.98)	0.20
Chemotherapy (versus not)	1.76 (1.16–2.67)	0.01	1.88 (1.17–3.03)	0.01

HR, hazard ratio; CI, confidence interval; RT, radiation therapy.

Table 4
Comparative 2-year & 5-year survival rates; present study versus National Cancer Data Base (NCDB) (7, 8).

Sub-site	Stage	2-Year overall survival (OS)		5-Year overall survival (OS)	
		Present study % OS (no. of patients)	NCDB	Present study % OS (no. of patients)	NCDB
Glottic larynx	I	92% (142)	88% (6698)	79% (142)	71% (6698)
	II	84% (120)	80% (1968)	66% (120)	59% (1968)
	III	63% (40)	67% (1199)	48% (40)	45% (1199)
	IV	63% (11)	54% (1094)	36% (11)	36% (1094)
Oral cavity	I	83% (99)	87% (4660)	68% (99)	72% (660)
	II	79% (103)	76% (3310)	58% (103)	58% (3310)
	III	55% (92)	61% (2239)	36% (92)	44% (2239)
	IV	37% (117)	47% (5431)	25% (117)	32% (5431)
Nasopharynx	I	NA (3)[a]	81% (170)	NA (3)[a]	61% (170)
	II	86% (15)	75% (327)	60% (15)	56% (327)
	III	77% (34)	70% (408)	59% (34)	56% (408)
	IV	60% (70)	52% (759)	31% (70)	34% (759)
Non-glottic larynx	I	84% (19)	76% (1162)	63% (19)	50% (1162)
	II	80% (41)	75% (1544)	31% (70)	34% (759)
	III	71% (49)	68% (1875)	43% (49)	45% (1875)
	IV	48% (86)	52% (3010)	30% (86)	29% (3010)
Oropharynx	I	92% (28)	82% (4282)	50% (280	60% (4284)
	II	80% (65)	69% (2983)	54% (65)	47% (2983)
	III	57% (121)	55% (1968)	41% (121)	36% (1968)
	IV	30% (115)	44% (5018)	17% (115)	27% (5018)
Hypopharynx	I	40% (10)	69% (297)	30% (10)	45% (297)
	II	75% (8)	57% (598)	50% (8)	31% (598)
	III	44% (43)	55% (906)	19% (43)	29% (906)
	IV	21% (63)	37% (2599)	3% (63)	20% (2599)

[a] The patient number is too small for accurate survival analysis & comparison.

cases extracted during similar period from the National Cancer Data Base (NCDB) [7,8]. NCDB is a nationwide oncology outcomes database for more than 1500 Commission-accredited cancer programs in the United States, and is recognized as the largest clinical registry in the world.

Statistical methods

Descriptive statistics were used to describe patient, tumour and treatment characteristics. Overall survival (OS) and HNC specific survival (HNCSS) were the co-primary endpoints of this study which were measured from the date of histological diagnosis to the patients' death from any cause or HNC related death, respectively. Patients who were still alive at this time were considered as censored cases. Two-year, 5, 10, 15 and 25-year OS & HNCSS of the whole cohort and of each anatomical site were obtained by the Kaplan–Meier method and the significance of differences between curves as classified by variable category was evaluated by the log-rank test on univariate analysis. Cox proportional hazards model was used for multivariable analysis (MVA) to estimate the simultaneous impact of patient, tumour and treatment related factors on survival outcomes. All p values were two-sided with $p \leqslant 0.05$ considered significant. This study was statistically analyzed on SPSS software (version 14.0; SPSS, Inc., Chicago, IL).

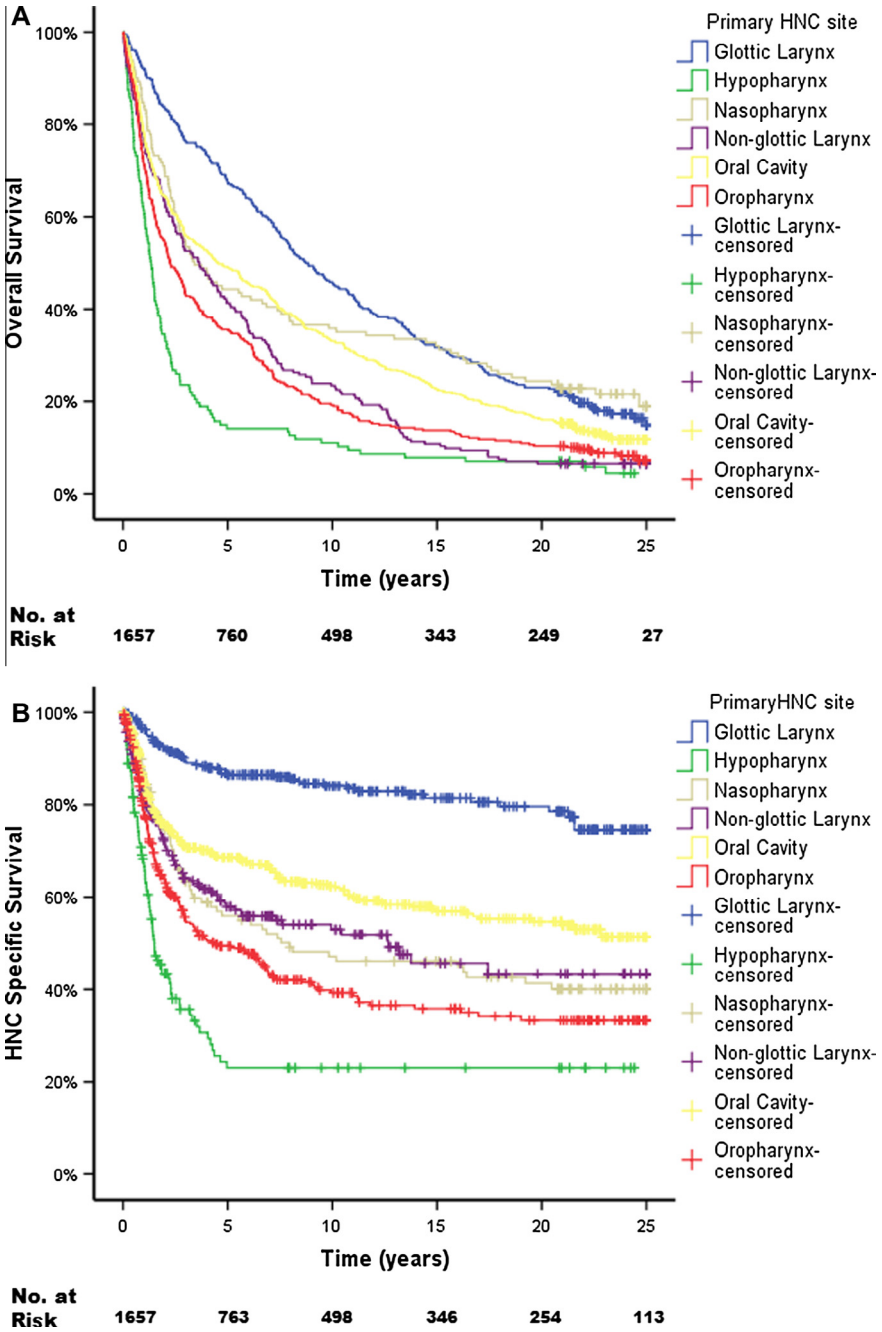

Fig. 1. Primary head and neck cancer Kaplan–Meier (A) overall survival and (B) head and neck cancer (HNC) specific survival analysis across different primary sites.

Results

Patient characteristics

A total of 1657 consecutive patients of primary HNC were identified over a period of diagnosis from January 1986 to December 1990. The main clinico-pathological findings are summarized in Table 1. Men were commonly affected with HNC in our study (p-0.001), and showed a high incidence of glottic and hypopharyngeal HNC. Overall, females had higher occurrence of nasopharynx (29.8%) and oropharyngeal HNC (28.7%). Patients with HNC of the nasopharynx had a relative younger presentation (median age, 50 years) than other primary HNC sites (median age, 63–65 years), $p < 0.001$.Thirty-seven percent of the HNC patients had early stage I–II disease at presentation, while 45% had loco-regionally advanced but resectable disease (stage III–IVA). Seven percent of the whole group had advanced unresectable (stage IVB–IVC) disease at the time of diagnosis. Patients with glottic cancer were diagnosed more often with early stage I–II disease (88.7%) than patients with cancer of any other site. Chemotherapy was only prescribed to 1.9% of the HNC patients in this era.

Survival

Mortality figures from all causes and HNC specific are presented in Table 2. There was a statistically significant difference in overall survival ($p < 0.001$) and HN cancer specific survival ($p < 0.001$) among the different HNC primary sites (Table 2). This was confirmed on univariate Kaplan–Meier survival analysis (Fig. 1). Multivariate Cox proportional hazard models for patients with HNC in this study are presented in Table 3. Disease stage at presentation and HNC in oropharynx and hypopharyngeal sites were

significantly related to poor overall survival and HNC specific survival ($p < 0.001$, Table 3). Table 4 comparatively summarizes the 2 and 5-year overall survival rates in relation to the NCDB database outcomes.

Discussion

This long term population-based study can serve as a reference for clinicians and researchers. It demonstrates the variations in HNC survival across different primary sites. In addition, HNC specific causes of death appear relatively uncommon after five years. Furthermore, HNC specific survival is markedly superior to overall survival, which we hypothesize is secondary to smoking related comorbidities in this population.

In this study, males were more frequently diagnosed with glottic cancer, while females were more often affected with nasopharynx & oropharyngeal HNC. This gender variance is consistent with reported literature and might be related to differences in smoking rates, infections, and genetic susceptibility [9–11]. Our data are consistent with studies involving UK HNC patients and SEER data from the United States, which report a figure of 45–47% for advanced stage presentation in HNC patients [12,13]. In contrast, our results shows significantly lower proportion of advanced stage than reports from other parts of the non-western world [14,15]. This referenced literature from Asia and Brazil report a high incidence of 66–80% advanced stage presentation for HNC in their population. Limited healthcare resources in developing nations are one of the probable reasons for this late stage presentation [16].

Current management of HNC favors multimodality approach but is still complex, and often deals with issues related to morbidity and quality of life. With an ever increasing focus on organ preservation, concurrent chemoradiation (CRT) therapy has become the standard of care in most of HNC primary sites. Several trials and meta-analysis have demonstrated improved survival rates with the use of chemoradiation therapy [17,18]. The role of CRT as adjuvant in high-risk patients following surgery is validated [19]. Our patient analysis is from a historic era of 1986–1990 when CRT was not adopted as a routine treatment protocol, and chemotherapy was prescribed in only 1.9% of the study population. The intent of chemotherapy in our cohort was potentially palliative in nature, as supported by the high hazard ratio on multivariable analyses (Table 3).

Over the last decade, there has been a considerable improvement in diagnosis, staging and treatment of HNC, and overall the natural history of HNC has also evolved. The increasing incidence of human papillomavirus (HPV)-related HNC has considerably modified their natural history [10,11]. In particular, about 40–50% of oropharyngeal cancers in this historical study population might be attributable to HPV, while current studies link HPV to about 70–80% of these cancers in the developed world, with more affinity for younger age group [20]. This has considerable future clinical implications in form of a growing burden of young patients with good performance status and superior survival [20,21]. This study demonstrated a significantly poor survival rates for oropharyngeal cancers diagnosed about 2 decades ago (Table 3). The result of this study should be considered in the context of its strengths and limitations. It is limited by the retrospective nature of the study, missing staging information in a small proportion of individuals, information on comorbidities and performance status, and lack of follow up status, in terms of recurrence or definitive cause of mortality. These diverse issues reflect the pitfalls and limitations in collection and interpretation of this cancer registry's database. Further, the results of this study from a historical pool have to be cautiously interpreted. The outcome analysis from this historical dataset from the late 1980s and early 1990 might not be applicable to current treatment paradigms in the developed world. However, this large population based analysis with a long follow-up of 25 years is sufficiently powered to identify the association between survival and multiple patient and tumour characteristics, and is free from selection bias.

Conclusions

This population-based study of 1735 patients followed up for 25 years demonstrates the variation in survival by primary tumour site. In addition, it demonstrates that head and neck cancer specific death is most common in the first 5 years, and is subsequently dominated by competing causes of mortality. These results are useful as a reference tool for clinicians, researchers, and trainees.

Conflict of interest

None of the authors have a conflict of interest to declare.

Acknowledgement

Poster presentation at ASTRO's 54th Annual Meeting in Boston, MA on October 28–31, 2012.

References

[1] Mehanna H, Paleri V, West CM, et al. Head and neck cancer – Part 1: Epidemiology, presentation, and prevention. BMJ 2010;341:c4684.
[2] BC Cancer Statistics [Internet]. British Columbia: BC Cancer Agency; c2013. <http://www.bccancer.bc.ca/HPI/CancerStatistics/FF/cancercases.htm> [updated 26.04.2013; cited 18.02.2013].
[3] Laramore GE, Scott CB, al-Sarraf M, Haselow RE, Ervin TJ, Wheeler R, et al. Adjuvant chemotherapy for resectable squamous cell carcinomas of the head and neck: Report on Intergroup Study 0034. Int J Radiat Oncol Biol Phys 1992;23(4):705–13.
[4] Attar E, Dey S, Hablas A, Ramadan M, Rozek LS, Soliman AS. Head and neck cancer in a developing country: a population-based perspective across 8 years. Oral Oncol 2010;46(8):591–6.
[5] Gloeckler Ries LA, Reichman ME, Lewis DR, Hankey BF, Edwards BK. Cancer survival and incidence from the Surveillance, Epidemiology, and End Results (SEER) program. Oncologist 2003;8(6):541–52.
[6] Fleming ID, Cooper JS, Henson DE, et al., editors. AJCC cancer staging manual, American Joint Committee on Cancer. Philadelphia: Lippincott-Raven; 1997.
[7] Bilimoria KY, Stewart AK, Winchester DP, et al. The National Cancer Data Base: a powerful initiative to improve cancer care in the United States. Ann Surg Oncol 2008;15(3):683–90.
[8] Hoffman HT, Karnell LH, Funk GF, Robinson RA, Menck HR. The National Cancer Data Base report on cancer of the head and neck. Arch Otolaryngol Head Neck Surg 1998;124(9):951–62.
[9] Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011;61(2):69–90.
[10] Curado MP, Hashibe M. Recent changes in the epidemiology of head and neck cancer. Curr Opin Oncol 2009;21(3):194–200.
[11] Heck JE, Berthiller J, Vaccarella S, Winn DM, Smith EM, Shan'gina O, et al. Sexual behaviours and the risk of head and neck cancers: a pooled analysis in the International Head and Neck Cancer Epidemiology (INHANCE) consortium. Int J Epidemiol 2010;39(1):166–81.
[12] MacKenzie K, Savage SA, Birchall MA. Processes and outcomes of head and neck cancer patients from geographically disparate regions of the UK. A comparison of Scottish and English cohorts. Eur J Surg Oncol 2009;35(10):1113–8.
[13] Carvalho AL, Nishimoto IN, Califano JA, et al. Trends in incidence and prognosis for head and neck cancer in the United States: a site-specific analysis of the SEER database. Int J Cancer 2005;114(5):806–16.
[14] Mohanti BK, Nachiappan P, Pandey RM, Sharma A, Bahadur S, Thakar A. Analysis of 2167 head and neck cancer patients' management, treatment compliance and outcomes from a regional cancer centre, Delhi. India J Laryngol Otol 2007;12(1):49–56.
[15] De Paula AM, Souza LR, Farias LC, Corrêa GT, Fraga CA, Eleutério NB, et al. Analysis of 724 cases of primary head and neck squamous cell carcinoma (HNSCC) with a focus on young patients and p53 immunolocalization. Oral Oncol 2009;45(9):777–82.
[16] Overgaard J, Mohanti BK, Begum N, Ali R, Agarwal JP, Kuddu M, et al. Five versus six fractions of radiotherapy per week for squamous-cell carcinoma of the head and neck (IAEA-ACC study): a randomised, multicentre trial. Lancet Oncol 2010;11(6):553–60.
[17] Dansky Ullmann C, Harlan LC, et al. A population-based study of therapy and survival for patients with head and neck cancer treated in the community. Cancer 2012;118(18):4452–61.

[18] Bernier J, Cooper JS, Pajak TF, van Glabbeke M, Bourhis J, Forastiere A, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC and RTOG. Head Neck 2005;27(10):843–50.
[19] Blanchard P, Baujart B, Holostenco V, Bourredjem A, Baey C, Bourhis J, et al. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC): a comprehensive analysis by tumour site. Radiother Oncol 2011;100(1):33–40.
[20] Mehanna H, Beech T, Nicholson T, El-Hariry I, McConkey C, Paleri V, et al. Prevalence of human papillomavirus in oropharyngeal and nonoropharyngeal head and neck cancer – systematic review and meta-analysis of trends by time and region. Head Neck 2013;35(5):747–55.
[21] Chaturvedi AK, Anderson WF, Lortet-Tieulent J, Curado MP, Ferlay J, Franceschi S, et al. Worldwide trends in incidence rates for oral cavity and oropharyngeal cancers. J Clin Oncol 2013;31(36):4550–9.