Head and neck oncology experience in Makkah, Saudi Arabia

Ameen Z. Al-Herabi, FACS, FRCSC.

ABSTRACT

الأهداف: تقديم تجربتنا في مجال أورام الرأس والرقبة وتطوير قاعدة بيانات مكة الالكترونية المحلية في هذا المجال.

الطريقة: تم إجراء دراسة استطلاعية للحالات خلال الفترة أكتوبر 2007 ونوفمبر 2008 من المرضى الذين تم تشخيصهم بسرطان الرأس الرقبة ضمن قسم الأنف والأذن والحنجرة وجراحة الرأس والرقبة – مستشفى النور التخصصي – مكة المكرمة – المملكة العربية السعودية.

النتائج: تضمنت هذه الدراسة 44 مريض. كان هناك 24 ذكر (54.5%) و20 أنثى (45.5%). كان لدى 16 مريض (36.4%) سرطان تجويف شفهي. ولدى 10 مريض (22.7%) سرطان تحت البلعوم. ولدى 10 مَريض (22.7%) سرطان البلعوم الأنفي، ولدى 6 مريض (13.6%) سرطان الغدة الدرقية، وكما لدى 2 مريض (4.5%) سرطان الرقبة الثانوي مجهول المصدر. تم عرض 36 مريض (81.8%) بالمرحلة الثّالثة والرّابعة مقابل 8 مريض (18.1%) قدّموا بالمرحلة الأولى والثّانية(p=0.0016). تم علاج 24 مريض (54.5%) تم علاجهم أولياً بالجراحة، بينما 20 مريض (45.5%) تم علاجهم جراحياً بشكل غير أولي على شكل علاج إشعاعي (XRT) أو كيماوي. والمؤشرات هي 16 مريض (38%) كانوا خاليين من أيّ أورام، توفي 2 مريض (5%) في فترة ما بعد الجراحة، تم تشخيص الورم مرة أخرى لدى 2 مريض (5%)، وفقد 24 مريض (54%) المتابعة.

خاتمة: كُلّ الخدمات الورمية المتعلقة بمرضى سرطان الرأس والرقبة متضمناً ذلك الجراحة، والعلاج بالأشعة، والعلاج الكيمياوي يجب أن تكون في مركز أورام واحد من خلال قناة معيارية واحدة تحت مسمى وحدة أورام الرأس والرقبة لنتمكن من تقديم خدمة المرضى الموحدة ومتابعة ومراقبة كافية.

Objectives: To present our experience in head and neck cancer, and the development of our own local electronic Makkah Head and Neck Database.

Methods: A prospective collection of cases was conducted between October 2007 and November 2008 of patients diagnosed with head and neck cancer within the Department of Otolaryngology, Head and Neck Surgery at Al-Noor Specialist Hospital, Makkah, Kingdom of Saudi Arabia.

Results: Forty-four patients were included in this study. There were 24 males (54.5%), and 20 females (45.5%). Sixteen patients (36.4%) had oral cavity cancer, 10 patients (22.7%) had hypopharyngeal cancer, 10 patients (22.7%) had nasopharyngeal cancer, 6 patients (13.6%) had thyroid cancer, and 2 patients (4.5%) had neck secondary-unknown primary. Thirty-six patients (81.8%) presented with stages III and IV versus 8 patients (18.1%) with stages I and II (p=0.0016). Twenty-four patients (54.5%) were managed primarily by surgery, while 20 patients (45.5%) were managed primarily non-surgically in the form of external beam radiotherapy (XRT), or XRT/Chemotherapy. Outcomes were: 16 patients (38%) were free of any recurrence, 2 patients (5%) died in the perioperative period, 2 patients (5%) had loco-regional recurrence, and 24 patients (54%) were lost follow up.

Conclusion: All oncological services of head and neck cancer patients including surgery, radiotherapy, and chemotherapy should be provided in one oncology center, and managed through a standard one channel, namely, the Head and Neck Oncology Board, to achieve standard patient care, adequate follow up, and surveillance.

Saudi Med J 2009; Vol. 30 (10): 1316-1322

From the Department of Otolaryngology, Head & Neck Surgery, Umm Al-Qura University, and Al-Noor Specialist Hospital, Makkah, Kingdom of Saudi Arabia.

Received 19th July 2009. Accepted 1st September 2009.

Address correspondence and reprint request to: Assistant Professor Ameen Al-Herabi, Consultant, Department of Otolaryngology, Head & Neck Surgery, Umm Al-Qura University, Makkah, Kingdom of Saudi Arabia. Tel. +966 503832472. Fax. +966 (2) 5534088. E-mail: herabi@hotmail.com

Squamous cell cancer (SCC) of the head and neck is the sixth most common cancer worldwide, with a lifetime risk of 2% for men, and 0.6% for women.[1] In Western Europe, there are approximately 76,000, and in the United States of America (USA), there are also approximately 37,000 new cases of oral-cavity, pharyngeal, and laryngeal cancer diagnosed each year.[1] Malignant neoplasm of the head and neck region is most common in the fourth, fifth, and sixth decades of life.[2] The idea of developing an electronic database registry for head and neck cancer started with Fletcher and McManus in 1987[3] from Washington, DC, USA. This had evolved according to the development of the medical field and the computer systems.[4-6] The purpose of this study is to present our experience in head and neck cancer, and the development of our own local electronic database.

Methods. A total of 44 patients who met our inclusion criteria, and diagnosed with head and neck cancer were included in this study. This prospective study was conducted between October 2007 and November 2008, after the creation and development of the Makkah Head and Neck Database (MHND) (**Figure 1**) using Microsoft Access 2002 (Microsoft Corporation, Seattle, USA) as a collaboration project between Umm Al-Qura University and Al-Noor Specialist Hospital, a tertiary hospital in the holy city of Makkah, Kingdom of Saudi Arabia (KSA) after obtaining appropriate ethical and administrative approval. Coding of anatomical sites, staging, and morphology of tumors was carried out according to the American Joint Committee on Cancer (AJCC) Staging Manual, sixth edition 2002 guidelines.[7] Also, appropriate patients demographics, therapies, and outcomes were included in the MHND. The inclusion criteria of this prospective cohort study included all patients of both genders, and all age groups, once diagnosed with head and neck cancer within the Department of Otolaryngology, Head and Neck Surgery at Al-Noor Specialist Hospital, Makkah, KSA. Exclusion criteria included patients diagnosed with benign head and neck tumors, or any patients receiving major therapeutic intervention before presenting to our center. All data were recorded prospectively during the patient initial admission, and all follow up data were recorded during their out-patient clinic follow up. All patients treated with external beam radiotherapy (XRT) as a single modality, or adjunctive XRT (post operatively) were referred to Princess Noorah Oncology Center, King Abdulaziz Medical City, Jeddah, Kingdom of Saudi Arabia.

Data presented as mean ± SD for continuous variables, and as percentages for categorical variables. Group comparison was carried out using t test for continuous variables, and Chi-square test for discrete variables. The *p*-value was calculated using Fisher's exact, and a value of <0.05 was considered statistically significant. Relative risk (RR), and its 95% confidence interval (CI) were also presented when appropriate. Data analysis was carried out using Microsoft Excel 2002 (Microsoft Corporation, Seattle, WA), and SPSS version 11 (SPSS Inc., Chicago, IL, USA).

Results. The mean age was 49.55 ± 16.14 years, and a median of 46 years (age range: 31-88 years). There were 24 males (54.5%) with mean age of 52.17 ± 18.81, and 20 females (45.5%) with mean age of 46.40 ± 12.46, and with a male to female ratio of 1.2:1 with no significant statistical difference (p=0.83, RR=1.09, 95% CI: 0.721-1.663). There were 32 Saudi patients (72.7 %), and 12 non-Saudi (27.3 %) with a significant statistical difference (p=0.04, RR=1.58, 95% CI: 1.058 -2.385). Among the patients, 14 (32%) were smokers, and 30 patients (68%) were non-smokers with no significant statistical difference (p=0.12, RR=0.69, 95% CI: 0.459-1.044). The distribution of cancer is shown in **Table 1**. (**Figure 2** shows an example of a patient with oral cavity cancer) The most common pathology was SCC in 28 patients (63.7%), of which 20 patients (72%) were well-differentiated, 6 patients (21%) moderately-differentiated, and 2 patients (7%) poorly-differentiated. The second most common pathology was nasopharyngeal carcinoma (NPC) (8 patients [18.2%]), in which all were lymphoepithelioma, or World Health Organization (WHO) non-keratinizing type III.[7] Papillary thyroid carcinoma (PTC) accounted for 6 patients (13.6%). Lastly, 2 patients were diagnosed with lymphoma of nasopharynx, non-Hodgkin's large B-cell type. Only 2 patient presented as stage I disease, 6 patients (13.6%) had stage II disease, 14 patients (31.9%) had stage III disease, and 22 patients (50%) had stage IV disease. Most of the patients presented with late cancer staging (stages III & IV), 36 patients (81.9%) versus only 8 patients (18.1%) presented with early cancer staging (stages I & II), which was statistically very significant (p=0.0016, RR=1.93, 95% CI: 1.304-2.866). Types of therapy, surgical treatment, neck dissections, and reconstructive surgery of the patients are shown in **Table 2**. (**Figure 3** shows an example of a patient undergoing total thyroidectomy for PTC). (**Figure 4** shows an example of MRND). Regarding surgical complications, out of the 18 patients who had composite resection and/or neck dissection, 4 patients (22.2%) had post-operative wound infection, 4 patients (22.2%) had dysphonia and dysphagia, and 2 patients (11.1%) had skin fistula. (**Figure 5** shows an example of pectoralis major flap reconstruction). Out of the 6 patients who had total thyroidectomy,

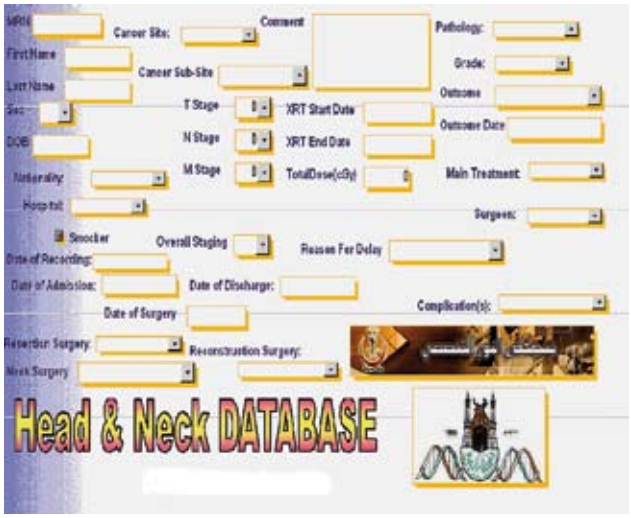

Figure 1 - The Makkah Head and Neck Database interface showing all included information.

Table 1 - Sites of the head and neck cancer of included study cases.

Sites	n	(%)
Oral cavity	16	(36.5)
Hypopharynx	10	(22.7)
Nasopharynx	10	(22.7)
Thyroid	6	(13.6)
Neck secondary unknown primary	2	(4.5)
Total	**44**	**(100)**

Table 2 - Types of therapy, surgical treatment, neck dissections, and reconstructive surgery of the head and neck cancer of the included study cases.

Variables	n	(%)
Primary therapy		
Surgery	24	
Composite resection/neck dissection	18	(75)
Total thyroidectomy	6	(25)
XRT or XRT/Chemotherapy	20	
Types of neck dissection		
Ipsilateral	10	(55.5)
Bilateral	8	(44.5)
Surgical techniques		
Functional	14	(54)
Modified radical	8	(31)
Radical	4	(15)
Types of reconstructive surgery		
Primary closure	4	(16)
Regional flaps	10	(42)
Deltopectoral	4	(40)
Pectoral major	4	(40)
Sternocleidomastoid	2	(20)
Free flaps	10	(42)
Radial forearm	4	(40)
Fibula	4	(40)
Iliac crest	2	(20)

XRT - external beam radiotherapy

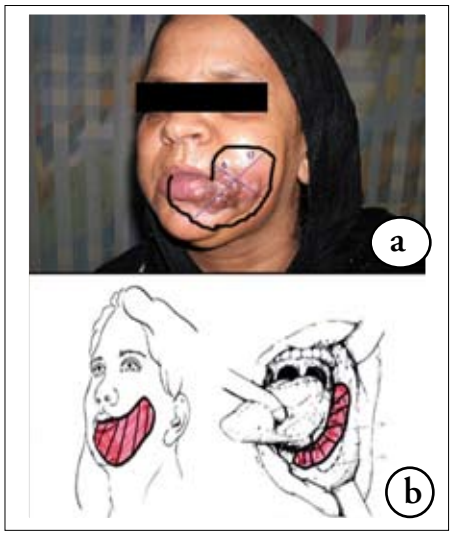

Figure 2 - A 48-year-old female with **a**) lower lip squamous cell cancer with cheek invasion, sized 6x17 cm, also **b**) perioperative surgical planning is demonstrated.

Figure 3 - Total thyroidectomy surgical planning for a patient diagnosed with papillary thyroid carcinoma. Shown on the frame the surgical specimen after removal.

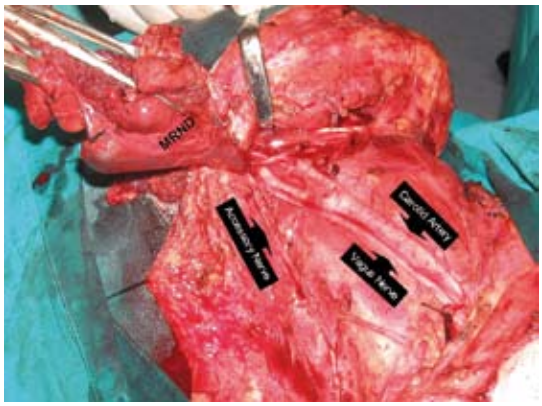

Figure 4 - Modified radical neck dissection (MRND) of a patient with oral cancer and neck metastasis demonstrating preservation of accessory nerve and scarify of internal jugular vein (IJV) and sternocleidomastoid muscle. The MRND specimen is shown only attached by IJV just before removal.

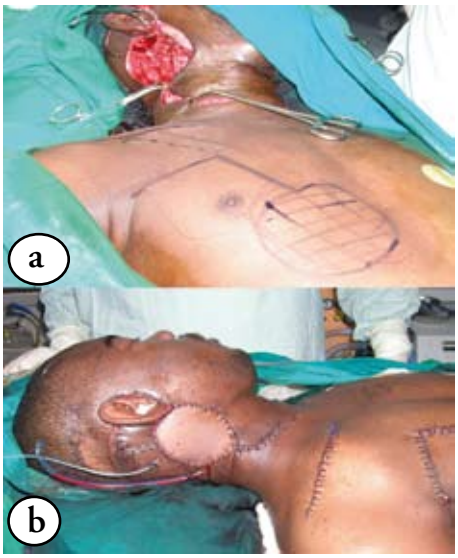

Figure 5 - Pectoralis major flap reconstruction **a**) before **b**) after, of a patient with appropriate defect.

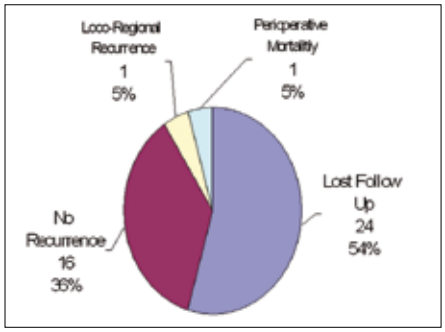

Figure 6 - Pie chart showing the distribution of patient's outcomes during the study period.

4 patients (66.6%) developed temporally transient hypocalcemia and hypo-parathyroidsm, of which none developed permanent hypo-parathyroidsm. No patient developed recurrent laryngeal nerve injury. On following up the patients during the study period: 16 patients were free of any recurrence, 2 patients died on the perioperative period due to tracheostomy and pulmonary complications, 2 patients had loco-regional recurrence, and 24 patients lost follow up after being sent for XRT in another institution (**Figure 6**), which was statistically very significant assuming the maximal accepted drop out rate for cancer patients is 15% (p=0.0003, RR=0.35, 95% CI: 0.176-0.686).

Discussion. At present, the multidisciplinary management of a head and neck cancer patient has become extremely complex. Medical information, diagnostic technology, and modes of therapeutic intervention available for treatment of head and neck cancer have increased exponentially.[3,4] The National Registry for Cancer has expanded and improved in recent years, and became a valuable tool in corporate and governmental planning. But, when it comes to rapid analysis of local patient's demographics, treatments, results, follow-ups, and outcomes, local electronic databases are the current best tool for the task. The MHND is our institution's model for cancer data management, where it is intended to provide an accurate system to identify risk factors, numbers of patients, types of treatment given, and outcomes. In our institution, head and neck cancer patients are treated within few surgical departments. Operative treatment of the head and neck cancer patients requires radical resection of the tumor. Therefore, the reconstruction and rehabilitation from a functional and aesthetic standpoint of view are essential goals of treatment; only secondary to control of the malignant disease and preservation of life.[8]

The mean age of the patients in our study was 49.55 ± 16.14, and median of 46 years (age range, 31-88 years). This agrees with Ahmed et al,[2] who stated that the malignant neoplasm are most common in the fourth, fifth, and sixth decades of life, and also agree with Issing et al,[8] who found that in 107 patients with advanced head and neck cancer, the average age was 59.4 years. Our male to female gender ratio was 1.2:1, which points toward male gender predominance, but less significant than another studies like Issing et al,[8] who had a 2.8:1 ratio. Other studies by McGuirt[9] had 2.1:1, and Adeyemi et al[10] had 1.8:1 ratios. In addition to a true incidence in the increase of head and neck cancer among females,[9,10] the likely reason for our higher number of female patients is the small study sample size, and inclusion of thyroid patients. Seventy-two percent (32 patients) were Saudi nationals, which is simply a reflection of accessibility of medical care in our center. The fictitious beneficial smoking effect (32% only were smokers) is due to the small sample size, as it is already established that smoking is a strong risk factor for head and neck cancer.[11] The most common head and neck cancers identified in Saudi Arabia were thyroid and nasopharyngeal cancers,[12,13] but in our study we had more aerodigestive cancers, which is possibly explained by increased smokeless (chewed) tobacco used in the Makkah region, and the small sample size.[14]

Pathologically, SCC accounts for 63.7% of identified malignancies in this series, and 94.4% of aerodigestive cancers. These results are compatible with D'Silva and Ward,[15] who stated that SCC accounts for more than 90% of malignancies of the oral cavity and oropharynx. Globally, SCC is one of the top 10 cancers with a predilection for older males.[4,9,10,15] Differentiation is a well-accepted independent factor in cancer prognosis.[15]

A study by Laramore et al[16] found that NPC-WHO non-keratinizing type-III represented 95.1% of the total NPC. This is the common endemic type with best prognosis.[17] Andejani et al[18] found that NPC represented >40% of the total head and neck cancers identified in KSA. In the head and neck region, lymphoma is a well-known pathology, which is known to occur extranodally in approximately 50% of cases, of which non-Hodgkin's large B-cell type represents 84% of the identified histological lymphoma types.[19] Thyroid cancer in this study accounts for 6 patients (13.6%), and all of them were PTC, which is comparable with the literature.[20]

Most of the patients presented with late cancer staging (stages III & IV), 36 patients (81.9%) versus only 8 patients (18.1%) presented with early cancer staging (stages I & II), which was statistically significant (p=0.0016). Ribeiro et al[21] from Brazil found that 93.4% of patients in his series of 46 patients with oral squamous cell carcinoma also presented late with clinical stages III & IV. It is well-established that staging at presentation represents one of the most important prognostic indicators.[22,23] There is increasing evidence that tumor stage, and therefore, prognosis and outcome are also determined significantly by the biology of the tumor.[24]

Sessions et al[25] managed 61% of 332 patients with oral tongue cancer with composite resection. The reason most oral cavity cancers are managed primarily surgically is the easy and efficient access of the mouth, therefore, small cancers are usually managed by surgery alone, and larger cancers are usually treated with composite resection followed by XRT/Chemo.[26,27] The 2 patients with neck secondary unknown (occult) primary were treated by neck dissection, and post-operative XRT of associated mucosal surfaces of nasopharynx, pharyngeal, and laryngeal axis after exhaustive unsuccessful search of the primary. From the largest published series in the literature regarding neck secondary unknown (occult) primary by the Danish Society of Head and Neck Oncology that included 352 patients, only 19% of the primaries were ever identified.[28] It is well-established that regardless of the neck nodal staging, neck treatment is essential in all oral cavity, especially tongue cancer including (T1 and T2) with deep invasion, T3, and T4. The universal neck treatment of T1 and T2 is still controversial.[29]

By the late 20th century, the concept of a more selective neck dissection over radical procedures was studied and developed.[30] The head and neck surgical defects after oncological resection of advanced carcinoma involving the oral cavity are often composite and involve bone, mucosa, soft tissues, and skin. Based on the good functional and aesthetic outcome and low rate of complications, the association of free and locoregional flaps represents a good reconstructive option for patients with extensive post-oncological composite head and neck defects.[31] Markkanen-Leppanen et al[32] addressed the quality of life of patients with pharyngeal and oral cancers post-microvascular reconstruction, and found that sociodemographic variables are more important that the type of the flap used. Also, it is clear in the head and neck surgical literature that reconstruction with plates only is not effective in bridging large defects of the resected mandible, and should be covered by a free flap, or a myocutaneous flap.[33] What really affect the prognosis of patients with oral and oropharyngeal cancer after surgical treatment is severe comorbidity, rather than the type of microvascular reconstruction.[34]

All 6 patients with PTC treated with total thyroidectomy and post operative RAI treatment. As total thyroidectomy for PTC greater than one cm in size yields the best outcome in terms of risk of recurrence and death.[35] The surgical treatment of PTC needs to be individualized based on the patient, tumor, and the experience of the surgeon to offer the best outcome.[35] Regarding surgical complications, out of the 18 patients who had composite resection and/or neck dissection, 4 patients (22.2%) had post-operative wound infection, 4 patients (22.2%) had dysphonia and dysphagia, and 2 patients (11.1%) had skin fistula.

In a study of 165 patients, the overall rate of wound infection was 41.8%.[36] Also, the factors significantly related to the likelihood of wound infection were tumor stage, previous chemotherapy, duration of pre-operative hospital stay, tracheostomy, and hypopharyngeal, and laryngeal cancers.[36] As for dysphonia and dysphagia, the addition of concurrent chemotherapy to XRT for locally advanced head and neck cancer resulted in increased long-term dysphagia. Early intervention using swallowing exercises, avoidance of nothing-by-mouth periods, and the use of intensity-modulated RT have been associated with better dysphagia rate.[37] Addressing fistulae formation in a study of 104 patients showed that fistula developed in 28.8% of patients. Recurrence, cancer stage, cancer location, and type of ablative surgery were identified as significant predictors of fistula formation.[38]

Out of the 6 patients who had total thyroidectomy, 4 patients (66.6%) developed transient hypocalcemia and hypo-parathyroidsm. Of which, none developed permanent hypo-parathyroidsm. No patient developed recurrent laryngeal nerve injury. Transient (4-37%) and permanent (1-7%) hypocalcemia are a well-recognized sequel of total thyroidectomy.[39-41] Regarding RLN injury, 1,974 RLN's dissected in thyroid surgery reported by Gong et al[42] had transient (1.6%), and permanent (0.5%) RLN injury. In studying the outcomes of patients during our study period, only 18 patients were accessible and available for follow up, of which 16 patients were free of

any disease (38% of total number of patients equivalent to 88.88% of available patients). Only 2 patients (5%) had loco-regional recurrence. Loco-regional recurrence rate is reported in the literature to be 12.3-22.8%.[43-45]

Addressing the issue of perioperative mortality, we had 2 patients (5%) who died in the perioperative period due to tracheostomy, and pulmonary complications. A study from the University of Iowa that carried out a national survey examining 24,803 patients found in-hospital mortality rate was 5.2%.[46] Another study examined 3943, and concluded a mortality rate of 2.9%, it found that major medical complications increased the odds of death by 5.65.[47] Postoperative pneumonia was the most common medical complication (3.3%), and was associated with a mortality rate of 10.9%. During the study period, 24 patients (54%) lost follow up after they had been sent for XRT in another center. A telephone survey of those 24 patients was attempted resulting in a result as follows: 16 patients were free of disease, 3 patients had recurrence, 2 patients died, and 3 patients were non-reachable. A study by Fang et al[48] also reported a high drop-out rate in a longitudinal study for patients with head and neck SCC (46% out of 149 patients). We feel a major contributing factor for our drop-out rate is related to the fact that all patients receiving post-operative XRT were referred to another center, and many of those patients continued their follow up in the other center.

The main limitation of this study was essentially related to the small sample size, no head and neck tumor board, no clear referral pathway for such patients, and non-availability of a radiation therapy center in our institution.

All head and neck cancer patients should be managed through a standard channel, namely, the Head and Neck Oncology Board. Also, the head and neck cancer care should be provided to all patients without any nationality restriction. Public education programs are essential tools to improve early presentation and treatment. All oncological services including surgery, radiotherapy, and chemotherapy should be provided in one oncology center to improve adequate patient care, follow up, and surveillance.

A prospective larger scale institutional electronic database is needed to improve local statistics, and therefore, decisions regarding patients care. A separate database should be implemented in the future for thyroid cancer patients, as they represent a different biology and behavior despite being regarded as head and neck cancer.

Acknowledgment. *The author gratefully acknowledges Dr. Badr Azab, and Dr. Rasha Lufy for their help in the data collection and statistical analysis.*

References

1. Saunders MI, Rojas AM. Management of cancer of the head and neck--a cocktail with your PORT? ***N Engl J Med*** 2004; 350: 1997-1999.
2. Ahmed Z, Azad NS, Rauf F, Yaqoob N, Husain A, Ahsan A, et al. Frequency of primary solid malignant neoplasms in different age groups as seen in our practice. ***J Ayub Med Coll Abbottabad*** 2007; 19: 56-63.
3. Fletcher MM, McManus CD. A computerized data management system for head and neck oncology. ***Laryngoscope*** 1987; 97: 1422-1429.
4. Mira E, Lanza L, Castelli A, Benazzo M, Tinelli C. [A computerized database for managing otorhinolaryngologic oncology patients] ***Acta Otorhinolaryngol Ital*** 1998; 18: 155-163. Italian.
5. Hambek M, Adunka O, Baghi M, Gstoettner W, Knecht R. AdOnco: a database for clinical and scientific documentation of head and neck oncology. ***Ann Otol Rhinol Laryngol*** 2006; 115: 144-149.
6. Birchall M, Brown PM, Browne J The organisation of head and neck oncology services in the UK: the Royal College of Surgeons of England and British Association of Head and Neck. Oncologists' preliminary multidisciplinary head and neck oncology audit. ***Annals of the Royal College of Surgeons of England*** 2003 85: 154-157.
7. American Joint Committee on Cancer. In: AJCC Cancer Staging Manual. 6th ed. New York (NY): Springer: 2002. p. 157-164.
8. Issing PR, Kempf HG, Heppt W, Schönermark M, Lenarz T. [Reconstructive surgery in the head-neck area with regional and free tissue transfer] ***Laryngorhinootologie*** 1996; 75: 476-482. German.
9. McGuirt WF. Head and neck cancer in women--a changing profile. ***Laryngoscope*** 1983; 93: 106-107.
10. Adeyemi BF, Adekunle LV, Kolude BM, Akang EE, Lawoyin JO. Head and neck cancer--a clinicopathological study in a tertiary care center. ***J Natl Med Assoc*** 2008; 100: 690-697.
11. Freedman ND, Abnet CC, Leitzmann MF, Hollenbeck AR, Schatzkin A. Prospective investigation of the cigarette smoking-head and neck cancer association by sex. ***Cancer*** 2007; 110: 1593-1601.
12. Ministry of Health. Health Statistical Year Book. Riyadh (KSA): Ministry of Health; 2006. p. 94-95.
13. al-Idrissi HY. Head and neck cancer in Saudi Arabia: retrospective analysis of 65 patients. ***J Int Med Res*** 1990; 18: 515-519.
14. Allard WF, DeVol EB, Te OB. Smokeless tobacco (shamma) and oral cancer in Saudi Arabia. ***Community Dent Oral Epidemiol*** 1999; 27: 398-405.
15. D'Silva NJ, Ward BB. Tissue biomarkers for diagnosis & management of oral squamous cell carcinoma. ***Alpha Omegan*** 2007; 100: 182-189.
16. Laramore GE, Clubb B, Quick C, Amer MH, Ali M, Greer W, et al. Nasopharyngeal carcinoma in Saudi Arabia: a retrospective study of 166 cases treated with curative intent. ***Int J Radiat Oncol Biol Phys*** 1988; 15: 1119-1127.
17. Yu KJ, Hsu WL, Chiang CJ, Cheng YJ, Pfeiffer RM, Diehl SR, et al. Cancer patterns in nasopharyngeal carcinoma multiplex families in Taiwan. ***Int J Cancer*** 2009; 124: 1622-1625.
18. Andejani AA, Kundapur V, Malaker K Age distribution of nasopharyngeal cancer in Saudi Arabia. ***Saudi Med J*** 2004; 25: 1579-1582.

19. Ezzat AA, Ibrahim EM, El Weshi AN, Khafaga YM, AlJurf M, Martin JM, et al. Localized non-Hodgkin's lymphoma of Waldeyer's ring: clinical features, management, and prognosis of 130 adult patients. ***Head Neck*** 2001; 23: 547-558.
20. Pelizzo MR, Merante Boschin I, Toniato A, Pagetta C, Casal Ide E, Mian C, et al. Diagnosis, treatment, prognostic factors and long-term outcome in papillary thyroid carcinoma. ***Minerva Endocrinol*** 2008; 33: 359-379.
21. Ribeiro AC, Silva AR, Simonato LE, Salzedas LM, Sundefeld ML, Soubhia AM. Clinical and histopathological analysis of oral squamous cell carcinoma in young people: a descriptive study in Brazilians. ***Br J Oral Maxillofac Surg*** 2009; 47: 95-98.
22. Carvalho AL, Nishimoto IN, Califano JA, Kowalski LP. 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: 806-816.
23. van der Schroeff MP, Baatenburg de Jong RJ. Staging and prognosis in head and neck cancer. ***Oral Oncol*** 2009; 45: 356-360.
24. Dhooge IJ, Albers FW, van Cauwenberge PB. Clinical characteristics and diagnostic delay of head and neck cancer: results from a prospective study in Belgium. ***Eur J Surg Oncol*** 1996; 22: 354-358.
25. Sessions DG, Spector GJ, Lenox J, Haughey B, Chao C, Marks J. Analysis of treatment results for oral tongue cancer. ***Laryngoscope*** 2002; 112: 616-625.
26. Campana JP, Meyers AD. The surgical management of oral cancer. ***Otolaryngol Clin North Am*** 2006; 39: 331-348.
27. Holsinger FC, Weber RS. Swing of the surgical pendulum: a return to surgery for treatment of head and neck cancer in the 21st century? ***Int J Radiat Oncol Biol Phys*** 2007; 69 (Suppl 2): S129-S131.
28. Grau C, Johansen LV, Jakobsen J, Geertsen PF, Andersen EV, Jensen BB. [Cervical lymphatic metastases from occult primary tumor. A nation-wide 20-year study from the Danish society of head and neck oncology] ***Ugeskr Laeger*** 2001; 163: 1432-1436. Danish.
29. Nouraei SA, Upile T, Al-Yaghchi C, Sandhu GS, Stewart S, Clarke PM, et al. Role of planned post-chemoradiotherapy selective neck dissection in the multimodality management of head and neck cancer. ***Laryngoscope*** 2008; 118: 797-803.
30. Ferlito A, Rinaldo A, Silver CE, Shah JP, Suarez C, Medina JE, et al. Neck dissection: then and now. ***Auris Nasus Larynx*** 2006; 33: 365-374.
31. Bianchi B, Ferri A, Ferrari S, Copelli C, Poli T, Sesenna E. Free and locoregional flap associations in the reconstruction of extensive head and neck defects. ***Int J Oral Maxillofac Surg*** 2008; 37: 723-729.
32. Markkanen-Leppanen M, Makitie AA, Haapanen ML, Suominen E, Asko-Seljavaara S. Quality of life after free-flap reconstruction in patients with oral and pharyngeal cancer. ***Head Neck*** 2006; 28: 210-216.
33. Mariani PB, LP Kowalski, J Magrin. Reconstruction of large defects postmandibulectomy for oral cancer using plates and myocutaneous flaps: a long-term follow-up. ***Int J Oral Maxillofac Surg*** 2006; 35: 427-432.
34. Borggreven PA, Kuik DJ, Langendijk JA, Doornaert P, de Bree R, Leemans CR. Severe comorbidity negatively influences prognosis in patients with oral and oropharyngeal cancer after surgical treatment with microvascular reconstruction. ***Oral Oncol*** 2005; 41: 358-364.
35. Bilimoria KY, Zanocco K, Sturgeon C. Impact of surgical treatment on outcomes for papillary thyroid cancer. ***Adv Surg*** 2008; 42: 1-12.
36. Penel N, Lefebvre D, Fournier C, Sarini J, Kara A, Lefebvre JL. Risk factors for wound infection in head and neck cancer surgery: a prospective study. ***Head Neck*** 2001; 23: 447-455.
37. Caudell JJ, Schaner PE, Meredith RF, Locher JL, Nabell LM, Carroll WR, et al. Factors associated with long-term dysphagia after definitive radiotherapy for locally advanced head-and-neck cancer. ***Int J Radiat Oncol Biol Phys*** 2009; 73: 410-415.
38. Andrades P, Pehler SF, Baranano CF, Magnuson JS, Carroll WR, Rosenthal EL. Fistula analysis after radial forearm free flap reconstruction of hypopharyngeal defects. ***Laryngoscope*** 2008; 118: 1157-1163.
39. Walsh SR, Kumar B, Coveney EC. Serum calcium slope predicts hypocalcaemia following thyroid surgery. ***Int J Surg*** 2007; 5: 41-44.
40. Karakas E, Osei-Agyemang T, Schlosser K, Hoffmann S, Zielke A, Rothmund M, et al. The impact of parathyroid gland autotransplantation during bilateral thyroid surgery for Graves' disease on postoperative hypocalcaemia. ***Endocr Regul*** 2008; 42: 39-44.
41. Chaudhary IA, Afridi ZD, Samiullah, Masood R, Mallhi AA. To ligate or not the inferior thyroid artery to avoid hypocalcaemia after thyroid surgery. ***J Ayub Med Coll Abbottabad*** 2007; 19: 19-22.
42. Gong RX, Zhang M, Luo SH, Zhou Y. [Safety of routine exposure of recurrent laryngeal nerve in thyroid surgery] ***Sichuan Da Xue Xue Bao Yi Xue Ban*** 2008; 39: 464-466. Chinese.
43. Alvarez Marcos CA, Llorente Pendas JL, Franco Gutierrez V, Fernandez Espina H, Alonso Guervos M, Suarez Nieto C, et al. [Tumour recurrence in squamous head and neck cancer] ***Acta Otorrinolaringol Esp*** 2007; 58: 156-163. Spanish.
44. Caudell JJ, Meredith RF, Spencer SA, Keene KS, Dobelbower MC, Bonner JA. Margin on Gross Tumor Volume and Risk of Local Recurrence in Head-and-Neck Cancer. ***Int J Radiat Oncol Biol Phys 2009*** April 20.
45. Leemans CR, Tiwari R, Nauta JJ, van der Waal I, Snow GB. Recurrence at the primary site in head and neck cancer and the significance of neck lymph node metastases as a prognostic factor. ***Cancer*** 1994; 73: 187-190.
46. Allareddy V, Konety BR. Characteristics of patients and predictors of in-hospital mortality after hospitalization for head and neck cancers. ***Cancer*** 2006; 106: 2382-2388.
47. Bhattacharyya N, Fried MP. Benchmarks for mortality, morbidity, and length of stay for head and neck surgical procedures. ***Arch Otolaryngol Head Neck Surg*** 2001; 127: 127-132.
48. Fang FM, Tsai WL, Chien CY, Chiu HC, Wang CJ, Chen HC, et al. Changing quality of life in patients with advanced head and neck cancer after primary radiotherapy or chemoradiation. ***Oncology*** 2005; 68: 405-413.