

Nasopharyngeal carcinoma in Saudi Arabia: clinical presentation and diagnostic delay

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السرطان الأنفي البلعومي في المملكة العربية السعودية: الاستعلان السريري والتأخر بالتشخيص ناصر الراجحي، مدحت السباعي، ياسر خفاجي، علي الزهراني، جمال محمد، عبدالله العمرو

الخلاصة: إن من الشائع أن يكون السرطان الأنفي البلعومي متفاقماً عند تشخيصه. وقد قيّم الباحثون في هذه الدراسة الاستعلان السريري للمرض وتأخر التشخيص والعوامل التي أثّرت على ذلك التأخير. وقد جمع الباحثون المعطيات استباقياً من 307 من المرضى الذين شخصوا حديثاً لإصابتهم بالمرض، وتضمّنت المعطيات تفاصيل ديموغرافية، وقصة المريض، والاستشارات في نطاق الرعاية الصحية، وعملية الإحالة. وقد صنّف الباحثون التأخر في التشخيص إلى تأخر يعود للمريض وتأخر يعود للأطباء وتأخر إجمالي. وقد صنّف الباحثون وجود كتلة بالحنق وإنسداد الأنف على أنها أكثر أعراض الاستعلان شيوعاً، وكان هناك ترابط يُعتد به إحصائياً بين زمن التأخر لثلاثة شهور أو أكثر وبين المرحلة المتفاقمة. كما كان هناك ترابط بين عمر المريض والأعراض الأنفية وبين التأخر الإجمالي فقد تراكفت المرحلة السريرية (الإكلينيكية) المتفاقمة عند التشخيص مع مواصفات المريض الاجتماعية والديموغرافية. ويمكن لتثقيف الناس وتحسين خدمات الرعاية الصحية الأولية أن يؤديا لتشخيص أبكر.

ABSTRACT Nasopharyngeal carcinoma is commonly advanced at diagnosis. In this study we evaluated the clinical presentation, diagnostic delay and factors affecting delay in nasopharyngeal carcinoma. Data were collected prospectively for 307 newly diagnosed patients, including detailed demographic data, disease history, health care consultations and referral process. Diagnostic delay was classified as patient, professional and overall. Neck lump and nasal obstruction were the commonest presenting symptoms. There was a significant association between delay time of ≥ 3 months and advanced stage. Patient's age and otological symptoms were associated with increased overall delay time. Advanced clinical stage at diagnosis was associated with patients' sociodemographic characteristics.

Carcinome nasopharyngé en Arabie saoudite : tableau clinique et retard de diagnostic

RÉSUMÉ Lorsqu'un carcinome nasopharyngé est diagnostiqué, la maladie se trouve généralement à un stade avancé. Dans cette étude, nous avons évalué le tableau clinique de cette maladie, le retard au diagnostic et les facteurs ayant une incidence sur ce retard. Une collecte prospective de données (informations démographiques détaillées, histoire de la maladie, consultations médicales et processus d'orientation vers un service spécialisé) a été réalisée auprès de 307 patients récemment diagnostiqués. Le retard au diagnostic a été classé en trois catégories : lié au patient, lié au professionnel et global. Les manifestations cliniques les plus courantes étaient une grosseur au cou et une obstruction nasale. Il existait une association significative entre un retard de diagnostic ≥ 3 mois et un stade avancé. L'âge du patient et les symptômes otologiques étaient associés à un retard global élevé. Un stade clinique avancé au diagnostic était associé à certaines caractéristiques sociodémographiques des patients.

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Introduction

Head and neck cancers represent 6% of all malignancies diagnosed annually in Saudi Arabia and 33% of these are of nasopharyngeal origin, with an annual age-standardized incidence of 2.5 and 0.8 per 100 000 for males and females respectively [1].

Diagnosing nasopharyngeal carcinoma (NPC) at an early stage is a difficult task as it usually runs silently or with nonspecific symptoms. A low index of suspicion and the technical challenges of postnasal space examination may also preclude earlier diagnosis, resulting in presentation with locally advanced disease that adversely influences outcome [2–4]. In general, delay in the diagnosis and treatment of NPC can be attributed to patient delay in seeking medical advice or to professional delay, which includes failure to identify the signs and symptoms suggestive of cancer, time waiting for hospital appointments and time waiting for referral to tertiary care centres.

The aim of our study in Riyadh, Saudi Arabia was to determine the time lapse between the onset of tumour-related symptoms and the time of presentation to the tertiary care centre to identify the factors contributing to NPC diagnostic delay and to evaluate the impact of delay on tumour staging.

Methods

Study design and patient population

A hospital-based prospective study was done with all newly diagnosed, untreated patients with NPC who attended the combined head and neck oncology outpatient clinic at King Faisal Specialist Hospital and Research Centre (KFSH&RC) between January 2000 and December 2003. Structured, face-to-face interviews were performed by a medical doctor. The interview contained detailed questions concerning demographic

data, level of education, history of disease from onset of the patient's first symptoms to definite diagnosis, number of physicians involved, availability of health services and referral process. Informed consent for treatment was signed by all patients.

Data regarding tumour stage and histopathological type were obtained from a prospectively collected NPC database. The American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) tumour node metastasis (TNM) classification and stage grouping was used [5].

Measures of delay

Patient-dependent delay was measured from the onset of symptoms to initial health care consultation. Professional-dependent delay was calculated from the date of first medical consultation to the date of presentation at our institution; this included time spent for work-up, establishing the pathological diagnosis and the referral process. The total delay was the sum of patient and professional delays.

Statistical analysis

Summary statistics for continuous variables are presented using median and range. The chi-squared test was used to test the association between categorical variables. For the purpose of statistical analysis, patients were classified according to age (< 65 years or 65+ years) and education level [high (university graduate or higher degree) or low (all others)]. Odds ratios (OR) and confidence intervals (CI) were estimated for all independent variables using logistic regression.

Results

Study population and presentation

During the study period, 307 patients with the diagnosis of NPC were included; their characteristics are summarized in Table

1. The median age was 46 years (range 12–85), with a male to female ratio of 3:1.

The majority of patients had advanced disease (stage III and IV) at the time of evaluation (79.2%), and many had cranial nerve involvement (19.2%) and distant metastasis (12.4%). Fewer females had stage IV presentation: 55.8% (43/77) compared with 68.7% (158/230) for males ($P = 0.04$). In this cohort of patients 20.5% were university graduates or had a higher degree education; this was significantly higher among males (24.3%) compared with females (9.1%) (P

$= 0.004$). Neck lump and nasal obstruction were the commonest presenting symptoms (61.6% and 54.7% respectively).

Diagnostic delay

Overall, 88.6% of our patients were judged as delayed (3 months or more from onset of symptoms to diagnosis): 109 (35.5%) by 3–6 months and 163 (53.1%) by > 6 months. The overall median delay time was 6.5 months (range 0.5–63). The time elapsed from onset of symptoms to initial health care consultation, diagnostic work-up and the referral process to tertiary hospital are presented in Table 2. Most of the delay was due to prolonged time spent between the initial health care visit and establishing the diagnosis (median 3 months, range 0–51).

Lack of patient awareness of the seriousness of the symptoms or treatment for a benign condition were the main factors causing delay, in 26.7% and 58.6% of cases respectively (Table 3). Most patients were seen by more than 1 physician for their complaint before the diagnosis was established (median 3 physicians, range 2–8).

The median time to initiate therapy for the 282 patients treated was 3 weeks (range 1–8 weeks), with 89% of patients starting within 5 weeks from first evaluation at the hospital.

Effect of time delays and contributing factors

There was a significant association between a time delay of 3 months or more (diagnostic, professional and overall) and presentation with advanced stage tumour (III or IV). However patient-related delay time was not associated with stage (Table 4).

Patient's age < 65 years and presentation with otological symptoms were the only significant factors associated with the overall delay time ($P = 0.01$ and 0.02 respectively). Other contributing factors for delay are summarized in Table 5.

Table 1 Characteristics of patients at presentation with nasopharyngeal carcinoma (n = 307)

Characteristic	No.	%
<i>Age (years)</i>		
< 65	282	91.9
≥ 65	25	8.1
<i>Sex</i>		
Male	230	74.9
Female	77	25.1
<i>Level of education</i>		
Low	244	79.5
High	63	20.5
<i>Nationality</i>		
Saudi	290	94.5
Non-Saudi	17	5.5
<i>Presenting symptoms</i>		
Headache	110	35.8
Nasal obstruction	168	54.7
Nasal bleeding	144	46.9
Neck mass	189	61.6
Visual symptoms	29	9.4
Decreased hearing	139	45.3
<i>Stage of cancer</i>		
I	11	3.6
II	53	17.3
III	42	13.7
IV	201	65.5
<i>Cranial nerve involvement</i>	59	19.2
<i>Systemic metastasis</i>	38	12.4

Table 2 Patterns of delay in diagnosis for patients with nasopharyngeal carcinoma (n = 307)

Delay	Median (months)	Range (months)
<i>Type of delay</i>		
Patient delay	1.0	0–48
Diagnostic delay	3.0	0–51
Referral delay	0.5	0–36
Professional delay	4.0	0.25–58
Total	6.5	0.5–63
<i>To start of therapy^a</i>	0.75	0.25–2
<i>Stage of cancer</i>		
I & II	5	0.5–59
III & IV	7	0.75–63
<i>Presenting symptoms</i>		
Headache	5	< 1–36
Nasal obstruction	6	< 1–60
Nasal bleeding	5	< 1–24
Neck mass	5	< 1–48
Visual symptoms	3	< 1–18
Decreased hearing	5	< 1–60

^aFor 282 patients treated.

Discussion

KFSH&RC is the main tertiary referral centre for more than 300 public hospitals and private clinics in Saudi Arabia, and includes a national cancer treatment centre for the country. Most of our patients lived at a considerable distance from KFSH&RC with a median distance of 400 km. Free transportation and air tickets are provided by the health care system for cancer patients from anywhere in the country.

In the absence of specialized health care facilities and long distances separating the patients from tertiary care, many patients are diagnosed and treated late in the course of their disease. This was indicated by the fact that the majority of our patients (79.2%) were diagnosed with advanced stage and with systemic spread of cancer in 12.4% of

the cases. This finding corresponds well to a reported series from south-east Asia [6].

Patient-dependent factors resulting in diagnostic delay are usually related to a long elapsed period from the onset of symptoms to seeking medical advice, refusing work-up investigations or defaulting on follow-up visits after diagnosis [2]. In our study, few patients (3.9%) defaulted on conventional treatment, preferring alternative medicine.

The presentation of NPC is varied but the most commonly reported symptoms are neck lump and nasal symptoms [6–9]. Our data confirmed this pattern of presentation with neck mass and nasal symptoms being the leading causes for patients to seek medical advice. The age distribution and sex ratio of our cohort of patients are similar to other reported series [6–8].

In contrast to Lee et al. who reported that women and older age groups were more likely to be delayed [8], we did not detect any difference based on sex. Interestingly, the only adverse factors significantly associated with diagnostic delay were age younger than 65 years and presentation with otological symptoms. This could be attributed to the fact that otological symptoms may pose diagnostic difficulty resulting in delayed diagnosis [7,8,10]. Older people are more likely to visit their physician frequently for other medical problems.

Table 3 Factors causing delay in diagnosis for patients with nasopharyngeal carcinoma (n = 307)

Factor	No.	%
Treatment as benign condition	180	58.6
Lack of patient awareness	82	26.7
Work-up and tissue diagnosis	17	5.5
Referral process	14	4.6
Patient's use of alternative medicine	12	3.9
Other	10	3.3
No delay	35	11.4

Table 4 Effect of delay time on stage of cancer at presentation for patients with nasopharyngeal carcinoma (n = 307)

Type of delay/duration	Stage I-II (n = 64)		Stage III-IV (n = 243)		P-value	Odds ratio (95% CI)
	No.	%	No.	%		
<i>Patient delay (months)</i>						
< 2	39	23	134	77		1.0 ^a
≥ 2	25	19	109	81	0.40	0.78 (0.45–1.38)
< 3	42	21	161	79		1.0 ^a
≥ 3	22	21	82	79	0.92	1.02 (0.58–1.84)
<i>Medical diagnosis delay (months)</i>						
< 2	26	25	77	75		1.0 ^a
≥ 2	38	19	166	81	0.12	0.68 (0.38–1.20)
< 3	40	27	106	73		1.0 ^a
≥ 3	24	15	137	85	0.007	0.46 (0.26–0.82)
<i>Professional delay (months)</i>						
< 2	17	26	49	74		1.0 ^a
≥ 2	47	20	194	80	0.26	0.70 (0.37–1.32)
< 3	31	27	84	73		1.0 ^a
≥ 3	33	17	159	83	0.04	0.56 (0.32–0.98)
<i>Total delay (months)</i>						
< 2	5	36	9	64		1.0 ^a
≥ 2	59	20	234	80	0.16	0.45 (0.14–1.40)
< 3	13	37	22	63		1.0 ^a
≥ 3	51	19	221	81	0.01	0.39 (0.18–0.83)

^aReference category.

CI = confidence interval.

Diagnostic and patient delays are reported to influence treatment outcome and were found in some studies to be a predictor of survival in many cancers, including head and neck [11–13]. In a population-based German study on breast cancer, physician delay was identified as the main cause of delay in diagnosis, and there was a strong association between patient delay and stage at diagnosis for poorly differentiated tumours, suggesting that a substantial proportion of late-stage diagnoses could be avoided if all patients with breast cancer symptoms were seen by a doctor within 1 month [13].

In our study, 88.6% of the patients were delayed, with a median overall delay time

of 6.5 months. This is similar to the reported 7.2 and 8 months mean delay time in other Asian studies of NPC [2,8]. Unlike other types of cancer, NPC can pose a great diagnostic challenge. Even in the presence of specific symptoms, the nasopharynx is a difficult region to assess, and early inconspicuous NPC can be easily missed by inexperienced clinicians or by the use of conventional tools of examination [2]. In our patients, professional delay was the main contributor to overall time delay, particularly the time spent in establishing histological diagnosis.

Detecting NPC at an early stage is believed to be an important factor affecting

Table 5 Factors affecting total delay time for patients with nasopharyngeal carcinoma (n = 307)

Factor	Delayed ^a (n = 272)		Not delayed (n = 35)		P-value	Odds ratio (95% CI)
	No.	%	No.	%		
Sex						
Male	203	88	27	12		1.0 ^b
Female	69	90	8	10	0.75	1.1 (0.49–2.64)
Age (years)						
≥ 65	18	71	7	29		1.0 ^b
< 65	254	90	28	10	0.01	3.5 (1.35–9.17)
Education						
Low	219	90	25	10		1.0 ^b
High	53	84	10	16	0.2	0.6 (0.24–1.33)
Headache						
No	170	86	27	14		1.0 ^b
Yes	102	93	8	7	0.09	2.0 (0.88–4.63)
Nasal obstruction						
No	120	86	20	14		1.0 ^b
Yes	152	91	15	9	0.15	1.7 (0.83–3.43)
Nasal bleeding						
No	141	88	22	12		1.0 ^b
Yes	131	91	13	9	0.22	1.6 (0.67–3.25)
Neck mass						
No	107	83	12	17		1.0 ^b
Yes	165	88	23	12	0.6	0.8 (0.38–1.68)
Visual symptoms						
No	244	88	34	12		1.0 ^b
Yes	28	97	1	3	0.2	3.9 (0.51–29.1)
Decreased hearing						
No	143	85	26	15		1.0 ^b
Yes	129	93	9	7	0.02	2.6 (1.17–5.77)

^aTotal delay time 3 months or more; ^bReference category. CI = confidence interval.

disease prognosis. Lee et al. reported a decrease in the likelihood of presenting with stage I–II diseases by 2% for every extra month delay in diagnosis [8].

Koivunen et al. reported a significant influence of patient delay, but not professional delay, on prognosis [11]. In his series of 18 patients with NPC, the median patient delay and professional delay time were 1 and 1.9 months respectively. In our cohort the median patient delay time was similar (1

month) but the professional delay was much longer (4 months).

There is a lack of information in the literature regarding the time cut-off at which patients with NPC are considered delayed and its impact on staging. In a large retrospective study from Hong Kong, patients who had symptoms for 6 months or longer before diagnosis had a significantly inferior outcome when compared with those who had a shorter delay in diagnosis, with a

10-year actuarial disease-specific survival of 42% versus 48% ($P < 0.001$) [8]. In our study, an overall delay time longer than 3 months was significantly associated with advanced clinical stage at diagnosis.

Our study has some limitations. In many instances the information gathered from the patients was not cross-checked with other sources (i.e. family members), which makes the data subject to recall bias.

In conclusion, advanced clinical stage at diagnosis for NPC is strongly associated with sociodemographic characteristics. Public education and improving primary

health care services would lead to earlier diagnosis. KFSH&RC has launched an educational programme based on outreach visits of expert oncologists to target practitioners involved in referring and treating cancer patients, as well as communities in different provinces. The objective is to enhance the physician's skills in identifying symptoms that could be related to cancer and increase public and physician awareness of cancer.

References

1. *Cancer incidence report: Saudi Arabia 1999–2000*. Riyadh, Saudi Arabia, National Cancer Registry Authority, 2004.
2. Leong JL, Fong KW, Low WK. Factors contributing to delayed diagnosis in nasopharyngeal carcinoma. *Journal of laryngology and otology*, 1999, 113(7):633–6.
3. Farias TP et al. Prognostic factors and outcome for nasopharyngeal carcinoma. *Archives of otolaryngology, head & neck surgery*, 2003, 129(7):794–9.
4. Lee AW et al. Treatment results for nasopharyngeal carcinoma in the modern era: the Hong Kong experience. *International journal of radiation oncology, biology, physics*, 2005, 15, 61(4):1107–16.
5. American Joint Committee on Cancer. *Manual of staging of cancer*, 5th ed. Philadelphia, JB Lippincott, 1997.
6. Indudharan R et al. Nasopharyngeal carcinoma: clinical trends. *Journal of laryngology and otology*, 1997, 111(8):724–9.
7. Lee AWM et al. Nasopharyngeal carcinoma—time lapse before diagnosis and treatment. *Hong Kong medical journal*, 1998, 4(2):132–6.
8. Lee AWM et al. Nasopharyngeal carcinoma—presenting symptoms and duration before diagnosis. *Hong Kong medical journal*, 1997, 3(4):355–61.
9. Dolan RW, Vaughan CW, Fuleihan N. Symptoms in early head and neck cancer: an inadequate indicator. *Otolaryngology—head and neck surgery*, 1998, 119(5):463–7.
10. Low WK, Goh YH. Uncommon otological manifestations of nasopharyngeal carcinoma. *Journal of laryngology and otology*, 1999, 113(6):558–60.
11. Koivunen P et al. The impact of patient and professional diagnostic delays on survival in pharyngeal cancer. *Cancer*, 2001, 92(11):2885–91.
12. Teppo H et al. Diagnostic delays in laryngeal carcinoma: professional diagnostic delay is a strong independent predictor of survival. *Head and neck*, 2003, 25(5):389–94.
13. Arndt V et al. Patient delay and stage of diagnosis among breast cancer patients in Germany a population based study. *British journal of cancer*, 2002, 86(7):1034–40.