Oral Cancer in Tehran, Iran: An approach for understanding disease burden

Katayoun Sargeran

Academic dissertation

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“Who can reveal the secret of his qualities?
Whose eyes can see his beauties?
The bird of thought cannot soar to the height of his presence.”

Sa'adi Shirazi (Iranian poet, 13th century A.D)

To all the people of my country
ABSTRACT


The present study investigated the burden of oral cancer in Tehran, Iran in terms of patient and tumour characteristics, survival rate, and delay in diagnosis, with the main focus on oral cavity cancers.

For exploring the characteristics of malignant oral tumours, data were obtained from records of 1042 patients diagnosed with invasive oral cancers during 1993-2003 in 30 major hospitals in Tehran. Data were analysed in three groups: tumours of the lips, oral cavity, and major salivary glands. For survival analysis, 470 primary oral cavity and 82 lip cancer patients diagnosed during 1996-2003 were followed from the date of diagnosis to late 2005.

To assess the time elapsed between patients’ first awareness of symptoms and the final diagnosis (diagnostic delay) 100 consecutive patients with primary squamous cell carcinoma (SCC) of the oral cavity who were referred to three university hospitals in Tehran during September 2004 to September 2006 were studied. Data were obtained by means of structured questionnaire-interviews and by reviewing the medical record of each patient. Diagnostic delay was analysed in two phases: 1) time from onset of symptoms to the patient’s first professional visit (patient delay) and 2) time from the first professional visit to the final diagnosis (professional delay).

At the time of diagnosis, most oral cavity cancer patients were at advanced stages. The overall five-year survival rates of patients with oral cavity and lip cancer were 30% and 62%, lower than rates reported from western countries. Oral cancer patients’ survival was negatively associated with tumour stage at diagnosis. Another determinant of patients’ survival was treatment modality. Patients treated with radiotherapy as the sole mode of treatment had lower survival rates than those treated with radiotherapy and surgery. The findings of this study revealed that the mean diagnostic delay was high (7.2 months, SD
In general, “patient delay” constitutes a substantial part of the total time elapsed between the onset of symptoms and diagnosis.

Based on the findings of this study, developing preventive programmes that focus on raising public awareness about the signs and symptoms of oral cancer is essential in promoting earlier diagnosis. In addition, health care professionals, especially dentists and oral hygienists, should be empowered to improve early diagnosis and gain better treatment outcomes for oral cancer patients in Tehran, Iran.

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LIST OF ORIGINAL PUBLICATIONS

The thesis is based on the following original articles referred to in the text by their Roman numerals.


III. Sargeran K, Murtomaa H, Safavi SM, Vehkalahti M, Teronen O. Survival after lip cancer diagnosis. Journal of Craniofacial Surgery (Accepted for publication)

## ABBREVIATIONS

<table>
<thead>
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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>CE</td>
<td>Continuing education</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>FOM</td>
<td>Floor of the mouth</td>
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<td>HPV</td>
<td>Human papilloma virus</td>
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<td>ICD</td>
<td>International Classification of Diseases</td>
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<td>OC</td>
<td>Oral cavity</td>
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<td>OR</td>
<td>Odds ratio</td>
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<tr>
<td>OSCC</td>
<td>Oral squamous cell carcinoma</td>
</tr>
<tr>
<td>QOL</td>
<td>Quality of life</td>
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<tr>
<td>SCC</td>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SES</td>
<td>Socio-economic status</td>
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<td>TCDOCP</td>
<td>The Crete Declaration on Oral Cancer Prevention</td>
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<tr>
<td>TNM</td>
<td>Tumour Node Metastasis</td>
</tr>
<tr>
<td>TSNA</td>
<td>Tobacco-specific nitrosamines</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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</tbody>
</table>
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1. INTRODUCTION

Cancer is one of the leading causes of death worldwide. Oral cancer, the most common cancer of the head and neck region (Stewart and Kleihues 2003), ranks eighth among the most prevalent cancers in the world (Petersen 2003a; Petersen et al. 2005). The incidence rate for oral cancers ranges from 0.1-31.5 per 100,000 of population per year (Moore et al. 2000; Parkin et al. 2002) with the highest rate reported from Melanesia (31.5 per 100,000 in men) and South Asia (12.7 per 100,000) (Parkin et al. 2005). Differences in incidence across countries are particularly explicable with reference to distinct risk profiles and etiological factors related to cultural and living conditions, lifestyles, and the implementation of preventive oral health programmes (Stewart and Kleihues 2003; Petersen et al. 2005; Parkin et al. 2005). The prevalence of oral cancers is higher among men, and the peak in occurrence is around the age of 60 (Silverman 2001; Gillison 2007). In recent decades, increases in the incidence rates have been reported from different parts of the world such as UK (Moore et al. 2000; Conway et al. 2006), Romania (Lung et al. 2007), Pakistan (Bhurgri 2005), Taiwan (Ho et al. 2002), and Brazil (Wünsch-Filho 2002).

Despite advances in technology and treatment the survival rate has not been improved in the last decades (Scully and Felix 2006). Oral cancer affects not only the quantity but also the quality of life (QOL) tremendously. Both oral cancer itself and its related treatments cause deformities in head and neck structures and several functional problems, due to the role of the oral cavity (OC) in the vital functions of speaking, eating, chewing, and swallowing (Rogers et al. 2007).

Oral cancer is associated with easily identifiable and detectable signs (Silverman 2001), which should facilitate its early diagnosis. Reducing delay in diagnosis and treatment improves the prognosis of oral cancers (Onizawa et al. 2003; Tromp et al. 2005b). Early diagnosis of oral cancer, with increasing rapidity of referral, and improving affected individuals’ access to multidisciplinary specialist care are priority topics in all health programmes encouraged by the World Health Organization (WHO) (Hobdell et al. 2003; Petersen 2005).
The major risk factors for oral cancers are tobacco and alcohol use. Oral health professionals are in a position that can highly influence and actively contribute to tobacco-cessation programmes (Petersen 2003b; Scully and Warnakulasuriya 2005). Dentists and other dental team members are the key personnel in reducing the incidence of oral cancer by identifying patients with high-risk behaviours and educating them about the consequences of their behaviour, and by early detection of potentially malignant and malignant lesions (Bsoul et al. 2005; Petti and Scully 2005; Scully et al. 2005).

The Islamic Republic of Iran covers an area of 1.6 million km². Its population is about 70 million, with an annual growth rate of 1.5%. The country is divided into 30 provinces and 842 districts, with approximately 67% of the population living in urban areas (Iran Statistical Year Book 2002). About half the whole population is under the age of 20 (Iran Statistical Year Book 2002), making Iran one of the youngest countries in the world (Pakshir 2004). A recent report indicates that cancer is the second most common cause of non-accidental death in Iran, after cardiovascular diseases (Sadjadi et al. 2007). According to the report of the Iran Ministry of Health and Medical Education in 2003 (IMOHE 2003), oropharyngeal cancers account for 3% of all cancers in Iran.

Integrating oral cancer information into national health surveillance systems and disease prevention programmes, such as programmes for the prevention of cancer and cardiovascular diseases with a focus on common risk factors, is emphasized by WHO as an objective for oral health 2020 (Hobdell et al. 2003). Implementation of any preventive programmes at the population level needs comprehensive assessment of the disease burden for the best allocation of resources, particularly in developing countries. The present study aimed, for the first time, to develop an approach to understand the burden of oral cancer in Tehran, Iran, by investigating patient and tumour characteristics, survival rate, and delay in diagnosis, with the main focus on oral cavity cancers.
2. REVIEW OF THE LITERATURE

2.1. Definitions, signs, and symptoms

Oral cancers are malignancies arising in the lip, tongue, floor of the mouth (FOM), gingiva, soft and hard palate, buccal/vestibular mucosa, oropharynx, and salivary glands, International Classification of Diseases (ICD) coding system, ICD-10 C00-C10 (WHO 2003). About 95% of all OC and lip cancers occur in people over age 40, and average age at the time of diagnosis is around 60 (Silverman 2003). Oral cancers usually are malignancies whose signs and symptoms can be recognized early. More than 90% of these cancers are carcinomas occurring in the stratified squamous epithelium lining these anatomical areas (Silverman 2001). Of the most common sites of involvement are the tongue, and lip. Oral cancer patients are always at risk for additional primary (second primary) neoplasms which may arise mainly in the aerodigestive tract (Braakhuis et al. 2002; Levi et al. 2006; Scully and Felix 2006).

Squamous cell carcinoma (SSC) typically presents as a persistent mass, nodule, or indurate ulcer. Colour changes in the squamous epithelium are common and are of red or red and white hues. Involvement of adjacent tissues is possible and represents local invasion of the tumour (Bsoul et al. 2005). For any single lesion with these features lasting more than three weeks SCC should be taken into consideration and it is an indication for urgent referral to a specialist (Scully and Felix 2006). Enlargement of a cervical lymph node may be detectable by palpation. Symptoms of oral cancer include swelling, pain, bleeding, and difficulty in opening the mouth, chewing, swallowing, and speech (Stewart and Kleihues 2003). Paresthesia and anaesthesia in the absence of a history of trauma are indicative of a malignancy. Symptoms are uncommon in earlier stages of the disease but become frequent with advanced local invasion (Bsoul et al. 2005). In more advanced stages, a large ulceroproliﬁrative mass, with areas of necrosis and extension to neighbouring structures such as bone, muscles, and skin may be evident (Stewart and Kleihues 2003). Metastasis occurs through the regional lymphatic pathways and distant metastases mostly spread to the lungs (Bsoul et al. 2005).
Some potentially malignant lesions are clinically identifiable. Of the most important ones are erythroplakia, leukoplakia, and lichen planus. These are characterized by increased risk for malignant development. The overall malignant transformation rate depends on degree of dysplasia and length of follow-up (Silverman et al. 1996). Because these lesions are generally without pain and discomfort, it is essential that people who have them be identified and kept under careful continuous clinical supervision (Scully 1995).

2.2. Epidemiology

2.2.1. Incidence

Of all diagnosed cancers, oral cancers account for 2-4% (Silverman 2001 and 2003). The incidence rate ranges from 0.1-31.5/100,000 of population per annum, with the highest rate reported from Melanesia and South Asia (Moore et al. 2000; Parkin et al. 2002). Oral cancer in South and South East Asia accounts for 58% of total worldwide cases (Nair et al. 2004). Compared with other western countries, an unexpectedly high incidence of oral cancer, exceeding 10/100,000 per year, has been reported from certain regions of France (Moore et al. 2000; Parkin et al. 2002; Downer 2007). Oral cancer incidence and mortality rates have increased in some parts of the world during the past decades, such as UK (Conway et al. 2006), Brazil (Wünsch-Filho 2002), and Taiwan (Ho et al. 2002).

Lip cancer is the most common malignancy among oral cancers in some parts of the western world, such as Australia (Moore et al. 1999 and 2001), Canada (Moore et al. 1999; Howell et al. 2003), Spain (Moore et al. 1999; Perea-Milla Lopez et al. 2003), and Finland (Moore et al. 1999; Tarvainen et al. 2004). In Asia, the incidence rates, ranging from 0 to 3%, are not as high as those reported for other oral cancers (Moore et al. 1999; Parkin et al. 2002). In general, the incidence rate of lip SCC is higher in Caucasian men (Lindqvist 1979a and b; Pukkala et al. 1994; Boyle 2001; Perea-Milla Lopez et al. 2003; Tarvainen et al. 2004).

For many countries, the tongue is reported to be the most dominant (20-40%) site of presentation of oral cancers within the OC (Gorsky et al. 2004). In India, the most prevalent site is the buccal mucosa, where the betel (the main risk factor for oral cancers in this area) is usually held (Warnakulasuriya and Ralhan 2007).
2.2.2. Survival

Cancers of the OC have high mortality rates, and despite current progress in cancer treatment, survival rates have not improved dramatically (Chen et al. 1999; Yeole et al. 2003; Bettendorf et al. 2004; Lam et al. 2006). The 5-year overall survival rates reported for several parts of the world have ranged from 2, when distant metastases exist (Yeole et al. 2003) to 95% (Shiboski et al. 2007) (Table 2.1.). Rates are extremely low for developing countries, mainly due to the advanced stages of tumour at the time of diagnosis. Local recurrence is the major cause of death (Woolgar et al. 1999).

Lip SCCs are less likely to cause mortality than are other cancers of the OC (Veness et al. 2001). The survival rate varies widely, depending on factors such as the stage of tumour at the time of diagnosis, on recurrences, and on regional neck node metastases (Table 2.1.). The highest survival rates, even up to 100%, have been reported for early stage tumours, whereas the rates decrease to 50% or less when regional spread or neck metastasis occurs. Most lip cancers are controlled successfully by complete surgical excision, but risk always remains for developing recurrent tumours that require repeated surgical resections (Zitch at al. 1995; de Visscher et al. 1999; McCombe et al. 2000; Babington et al. 2003).
Table 2.1. Five-year survival rates for oral cancer patients, reported from different parts of the world

<table>
<thead>
<tr>
<th>Author/ year</th>
<th>Location</th>
<th>Data collection period</th>
<th>N</th>
<th>Inclusion criteria</th>
<th>5-year survival rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Woolgar et al. 1999</td>
<td>UK</td>
<td>1989-1995</td>
<td>200</td>
<td>SCC(^1): Tongue, Buccal mucosa, FOM(^1), Gum, Retromolar, Alveolus, Oropharynx</td>
<td>Overall: 63%&lt;br&gt;By pathological TNM(^1) stage: I: 85%, II: 90%, III: 82%, IV: 42%</td>
</tr>
<tr>
<td>Laukkaa et al. 2003</td>
<td>Finland</td>
<td>1989-1995</td>
<td>174</td>
<td>SCC: OC(^4), Oropharynx, Hypopharynx</td>
<td>Overall: 32%, Cause-specific: 49%&lt;br&gt;By clinical TNM stage: I: 62%, II: 63%, III: 57%, IV: 40%&lt;br&gt;By site: tongue: 65%, other OC: 45%, oropharynx: 64%</td>
</tr>
<tr>
<td>Rautava et al. 2007</td>
<td>Finland</td>
<td>1988-1997</td>
<td>188</td>
<td>SCC: Tongue, Gingiva, FOM, hard palate, other OC sites</td>
<td>Overall: 38%, disease-specific: 58%</td>
</tr>
<tr>
<td>Mork and Glattre 1998</td>
<td>Norway</td>
<td>1953-1992</td>
<td>3640</td>
<td>Tongue, FOM, Other OC sites, Oropharynx</td>
<td>Relative survival rate&lt;br&gt;by site: Tongue &amp; FOM: 42%&lt;br&gt;Other OC sites: 44%, Oropharynx: 28%</td>
</tr>
<tr>
<td>Charabi et al. 1997</td>
<td>Denmark</td>
<td>1978-1982</td>
<td>156</td>
<td>OSCC(^5)</td>
<td>Overall: 37%&lt;br&gt;By clinical TNM stage: I: 61%, II: 32%, III: 16%, IV: 17%</td>
</tr>
<tr>
<td>Charabi et al. 2000</td>
<td>Denmark</td>
<td>1992-1996</td>
<td>304</td>
<td>OSCC</td>
<td>3-year survival rate: Overall: 42%&lt;br&gt;By clinical TNM stage: I: 58%, IV: 18%</td>
</tr>
<tr>
<td>Wutzl et al. 2007</td>
<td>Austria</td>
<td>1990-2000</td>
<td>222</td>
<td>SCC: OC, Oropharynx, Stages II-IV</td>
<td>Overall: 62%</td>
</tr>
<tr>
<td>Garzino-Demo et al. 2006</td>
<td>Italy</td>
<td>1989-2002</td>
<td>245</td>
<td>SCC: Tongue, Buccal mucosa, FOM, Gingiva</td>
<td>Overall: 64%&lt;br&gt;By clinical TNM stage: I: 80%, II: 78%, III: 48%, IV: 42%</td>
</tr>
<tr>
<td>Antoniades et al. 1995</td>
<td>Greece</td>
<td>1979-1989</td>
<td>408</td>
<td>Lip SCC</td>
<td>Overall: 83.3%&lt;br&gt;By clinical TNM stage: I: 92%, II: 68%, III: 40%, IV: 11%</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Years</td>
<td>Sample Size</td>
<td>Sites</td>
<td>Relative Survival</td>
</tr>
<tr>
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<tr>
<td>Carvalho et al. 2004</td>
<td>Brazil</td>
<td>1953-1997</td>
<td>3267</td>
<td>OC, Oropharyx, Lip excluded</td>
<td>Overall: 29% (1950s), 43% (1990s) By clinical TNM stage: Decade 50: I &amp; II: 53%, III &amp; IV: 24%, Decade 90: I &amp; II: 77%, III &amp; IV: 32%</td>
</tr>
<tr>
<td>Lo et al. 2003</td>
<td>Taiwan</td>
<td>1975-1996</td>
<td>378</td>
<td>SCC ICD-9 140-145</td>
<td>Overall: 56% By clinical TNM stage: I: 75%, II: 66%, III: 49%, IV: 30%</td>
</tr>
<tr>
<td>Chen et al. 2004</td>
<td>Taiwan</td>
<td>1987-1994</td>
<td>8114</td>
<td>ICD-9 140-149</td>
<td>Overall: 56%</td>
</tr>
<tr>
<td>Liu et al. 2006</td>
<td>Taiwan</td>
<td>1995-2002</td>
<td>1010</td>
<td>Lip, Oral tongue, FOM, Gingiva, Palate, Buccal mucosa, Retromolar</td>
<td>Overall: 63%</td>
</tr>
<tr>
<td>Chen et al. 2007</td>
<td>Taiwan</td>
<td>1985-1994</td>
<td>9039</td>
<td>ICD-9 140-141, 143-146, 148-149</td>
<td>Overall: 55%</td>
</tr>
<tr>
<td>Yeole et al. 2003</td>
<td>India (Bombay)</td>
<td>1992-1994</td>
<td>1808</td>
<td>ICD-10 C00-C06</td>
<td>Overall: 40%, By clinical extent: Localized: 59%, Regional: 16%, Metastasis: 2%</td>
</tr>
<tr>
<td>Bilkay et al. 2003</td>
<td>Turkey</td>
<td>1983-1999</td>
<td>118</td>
<td>Carcinoma, Lower lip</td>
<td>Overall: 73% , By clinical TNM stage: I: 100%, II: 94%, III: 67%, IV: 49%</td>
</tr>
<tr>
<td>Al-Rajhi et al. 2002</td>
<td>Saudi Arabia</td>
<td>1992-1998</td>
<td>57</td>
<td>SCC, Stage IV Tongue, Buccal mucosa, FOM, Retromolar, Alveolus</td>
<td>Overall: 20%</td>
</tr>
<tr>
<td>Inagi et al. 2002</td>
<td>Japan</td>
<td>-----------</td>
<td>221</td>
<td>SCC: Tongue, Buccal mucosa, FOM, Gingiva, Hard palate</td>
<td>By clinical TNM stage: I: 91%, II: 73%, III: 63%, IV: 47%</td>
</tr>
</tbody>
</table>

1 Squamous cell carcinoma  2 Floor of the mouth  3 Tumour Node Metastasis  4 Oral cavity  5 Oral squamous cell carcinoma  6 International Classification of Diseases
2.2.3. Aetiology and risk factors

Smoking and drinking are the main risk factors for head and neck cancers including oral cancer. Tobacco smoking and alcohol consumption separately and independently cause increased risk for oral cancer, and their combined use raises the risk expected with either exposure alone (Blot et al. 1988; La Vecchia et al. 1997; Gillison 2007; Hashibe et al. 2007). Many investigators have concluded that at least 75-80% of oral cancers are attributable to alcohol and tobacco exposure (Rodriguez et al. 2004; Gillison 2007; Hashibe et al. 2007).

Strong dose-response relationships appeared for each substance after controlling for exposure to the other (Blot et al. 1988; Hashibe et al. 2007). Oral cancer risk is related to both intensity and duration of alcohol and tobacco consumption. In an effort to understand the mechanisms of alcohol and tobacco interaction, what has been revealed is that the combined risk for oral and pharyngeal cancers is multiplicative or at least greater than additive (Blot et al. 1988; LaVecchia et al. 1997).

The aetiology of lip cancer is partly distinct from that of OC cancer. Chronic exposure to sunlight in the agricultural, forestry and fishing or any other out-door occupation, and smoking, particularly pipe smoking, are the major risk factors (Lindqvist 1979a and b).

2.2.3.1. Tobacco

Tobacco contains at least 50 known carcinogens, including polycyclic aromatic hydrocarbons such as tobacco-specific nitrosamines (TSNA) (Scully and Felix 2006; Gillison 2007). Age at starting smoking has an inverse relation to oral cancer risk (Llewellyn et al. 2004). Among ex-smokers, those who had quit smoking for more than ten years showed odds ratios (ORs) near to one for the OC cancers (La Vecchia et al. 1997).

Smokeless tobacco products have several carcinogens; these carcinogens are, however, fewer than those in smoking tobacco (Warnakulasuriya and Ralhan 2007). The high incidence of oral cancer in South Asia, especially the Indian subcontinent, is attributed to the use of smokeless tobacco products (Ahluwalia 2005). There are mainly two types of smokeless tobacco: chewing tobacco and snuff. Worldwide, several names are used for
different smokeless tobacco products, such as gutkha, nass, toombak, shamma, and moist snus (Warnakulasuriya and Ralhan 2007). Tobacco may also be added to areca nut or lime (calcium hydroxide). The areca nut or the betel nut can be chewed alone or as a quid. Although it is believed that the added tobacco plays the primary aetiological role in the development of oral cancer, areca products may play an independent role (Ahluwalia 2005).

Smokeless tobacco products differ greatly by region and culture. In the US, fermented moist snuff and fire-cured dry snuff have high levels of TSNA, whereas air-cured chewing tobacco is low in TSNA (Yen et al. 2007; Weitkunat et al. 2007). In Sweden, no association has been found so far, between intensity or duration of moist snuff use which is low in TSNA and oral cancer (Weitkunat et al. 2007).

2.2.3.2. Alcohol

Oral cancer risk significantly increases with both intensity and duration of alcohol consumption, and it may increase directly with alcohol concentration (Huang et al. 2003; Gillison 2007). Despite this, different studies suggest that all types of alcoholic beverages contribute to oral cancer risk, with ethanol as the common ingredient being responsible (Blot et al. 1988; La Vecchia et al. 1997; Altieri et al. 2004). Unexpectedly high incidence of oral cancer in certain parts of France has been attributed to an excessive consumption of crudely distilled spirit (Downer 2007). It has not yet been shown that alcohol itself is a direct carcinogen; it may, however, interfere with carcinogenesis by different mechanisms. Acetaldehyde the first metabolite of ethanol is a known carcinogen (Kurkivuori et al. 2007). Alcohol may also act as a solvent to increase mucosal exposure to carcinogens (Blot et al. 1988, La Vecchia et al. 1997, Gillison 2007). Heavy alcohol consumption is associated with nutritional deficiency, which may play a role in oral cancer incidence (Blot et al. 1988).

2.2.3.3. Other risk factors

Oral cancer can occur in non-smokers and non-drinkers, so other factors may also play a role in carcinogenesis. In the following lines some of these factors are discussed. Infection with Human papilloma virus (HPV) is one of the risk determinants of oral cancers, particularly those that involve the lingual and palatine tonsils within the oropharynx.
The estimated proportion of oral and oropharyngeal SCC attributable to HPV infection is 35% (Hansson et al. 2005). The vast majority of HPV-DNA-positive patients harboured HPV-16 (Hansson et al. 2005; Herrero et al. 2003). The degree to which oral HPV infection may contribute to increase risk for oral cancer with tobacco or alcohol use is currently unclear (Smith et al. 2004; Gillison 2007).

The relationship between diet and risk for oral cancer is well-established. It has been clearly shown that higher intake of fresh fruits and vegetables (La Vecchia et al. 1997; Franceschi et al. 1999; Bosetti et al. 2003; Guneri et al. 2005; De Stefani et al. 2005; Boeing et al. 2006; Pavia et al. 2006), and to some extent, olive oil (Franceschi et al. 1999, Bosetti et al. 2003), is associated with lower risk for oral cancer, after controlling for the effects of alcohol and tobacco. Various micro-nutrients, including vitamin C, beta-carotene, and flavonoids are also inversely related to oral and pharyngeal cancer risk, but generally less strongly than food groups (De Stefani et al. 2005; Gillison 2007). Total calories, saturated oil, eggs, and starchy foods have emerged increasing oral cancer risk (Franceschi et al. 1999, Bosetti et al. 2003).

It has been shown that poor oral health is associated with risk for oral cancer. Oral cancer risk is inversely associated with some measures of oral hygiene, such as frequency of tooth brushing and visits to a dental care provider (Moreno-Lopez et al. 2000; Guneri et al. 2005; Rosenquist et al. 2005). An independent role for oral hygiene was supported by significant elevations in oral cancer risk among non-smokers and non-drinkers with poor oral hygiene (Marshall et al. 1992).

2.2.4. Inheritance and genetic background

A positive family history such as having a sibling with oral cancer has been associated with increased risk for oral cancer (Gillison 2007). Conditions carrying increased risk for head and neck cancer include epithelial differentiation disorders, for instance dyskeratosis congenital and DNA repair deficiency syndromes such as Blooms’ syndrome, Fanconi anaemia, ataxia telangetasia, and xeroderma pigmentosum (Stewart and Kleihues 2003).
Cancer can be defined as uncontrolled tissue growth in susceptible patients, which results from an imbalance between cell division and programmed cell death (apoptosis). Oral cancers arise as a consequence of complex multi-step interactions between genetic susceptibility, behavioural factors such as tobacco use, and environmental factors such as viruses (Winn et al. 1998; Scully et al. 2000; Kang and Park 2001). Some genetic effects have been found in oral cancer patients but the exact process is not yet totally clear.

It has been shown that loss of specific chromosomal regions that contain tumour suppressor genes is an early predictor of subsequent progression of oral potentially malignant lesions to a cancer (Zhang and Rosin 2001). The p53 tumour suppressor gene mutations are the genetic errors most frequently found in oral cancer, and the p53 gene is a possible target for tobacco and alcohol (Jones 1998). Improved understanding of the underlying genetic events of oral cancer suggests promising advances in early detection, risk assessment, diagnosis, and prognostication, as well as novel approaches to treatment (Scully et al. 2000; Bagan and Scully 2008).

2.3. Detection

2.3.1. Early detection of oral cancers

Poor survival of oral cancer patients is, at least in part, due to failure in the early detection of small or potentially malignant lesions. Detection of oral cancer early is critical, because patients with early-stage tumours have considerably better survival rates than patients with advanced-stage tumours (Ship 2002). The treatment of oral cancer is expensive for the society, and the physical, psychological, and emotional impacts have considerable costs for the patients. Both morbidity and mortality associated with oral cancers can be reduced by early detection. These cancers are known to be amenable to early detection, because they mainly occur at sites that are visible and easily accessible to a painless, non-invasive examination, making early detection relatively simple (Silverman 2001; Petersen 2005).

The WHO encourages all health care systems to focus on the prevention and early detection of oral cancers as one of their main oral health targets. According to the Crete Declaration on Oral Cancer Prevention in 2005 (TCDOCP 2005), access to health facilities and provision of systems for early detection of oral cancers needs to be
strengthened worldwide, especially in countries with a high prevalence of oral cancers and in the developing world.

2.3.2. Diagnostic delay

Although oral cancers arise in anatomically accessible areas, delayed diagnosis is common (Stewart and Kleihues 2003). Diagnostic delay is usually defined as the time elapsed between onset of symptoms and final diagnosis (McLeod et al. 2005). Delay in diagnosis of oral cancers results in a reduction in survival and an increase in morbidity. The majority of patients first seek professional advice only when a tumour is already well advanced. The 5-year survival for small and localized tumours approaches 80% or higher but falls to 10% or less for stage IV disease (Table 2.1).

2.3.2.1. Patient delay

The time period from the presentation of symptoms to diagnosis or the “diagnostic delay”, is usually divided into two parts: “patient delay” and “professional delay” (McLeod et al. 2005). Patient delay is defined as the period between patient’s awareness of symptoms and the first visit to a professional. In many reports the whole diagnostic delay was mostly attributable to patient delay (Kowalski et al. 1994; Hollows et al. 2000; Kerdpon and Sriplung 2001a and b; Onizawa et al. 2003; Brouha et al. 2005), which does not necessarily mean that patients are solely responsible for it. Other factors such as access to health care services and patients’ psychological factors must be taken into consideration (Tromp et al. 2004 and 2005a; Diz Dios et al. 2005).

2.3.2.2. Professional delay

Professional delay is the time interval between a patient’s first consultation with a health care professional and the definitive diagnosis and reflects the delay in patients’ being referred to a specialist for confirmation by a histological diagnosis (McLeod et al. 2005). Professional delay can result from: failure on the part of the clinician to conduct a thorough examination, a low index of suspicion, and lack of experience with these tumours (Diz Dios et al. 2005).

Some studies show a difference between dentists and physicians in referring oral cancer patients, indicating that professional delay is longer in patients referred by dentists (Scully
et al. 1986; Kowalski et al. 1994). Paradoxically, other reports showed no significant association between the health care professional degree and the delay (Wildt et al. 1995; Kerdpon and Sriplung 2001b). However, several reports support the opinion that a dental care provider is more likely to detect a lesion during a routine appointment than is a medical provider (Gellrich et al. 2003; Lim et al. 2003; Holmes et al. 2003).

2.4. Prognosis

Advances in both surgical and non-surgical treatment of oral cancer have led to increased local tumour control in recent years. However, overall survival and mortality rates have not improved, due to advanced stage of tumour at the time of diagnosis, tumour recurrences at regional sites, and occurrence of secondary primary tumours and distant metastasis (Braakhuis et al. 2002; Marcus et al. 2004). Patients with oral SCC (OSCC) usually present with loco-regional disease, and the presence of distant metastasis at diagnosis is not considered a common event. In spite of aggressive treatment, i.e., wide tumour resection followed by radiotherapy and sometimes chemotherapy, tumour recurrence may occur in 18–76% of oral cancer patients (Kowalski et al. 2005). Of the lip cancer patients, 5–15% present with lymph node metastases, compared with more than 50–70% of those with tongue and FOM cancers (Stewart and Kleihues 2003).

2.4.1. Prognostic factors

Prognosis may be influenced by patient-related factors such as ethnicity (Scully and Bedi 2000, Shiboski et al. 2007), socio-economic status (SES) (Chen et al. 2007) and comorbidity (Ribeiro et al. 2000), tumour-related factors such as stage (Marcus et al. 2004; Kowalski et al. 2005), histological grade (Keski-Säntti et al. 2007), and vascular or peri-neural invasion (Bettendorf et al. 2004), and treatment-related factors (Kowalski et al. 2005). Among these different factors there may exist interactions of various strengths.

2.4.1.1. Patient-related factors

Notable differences exist in oral cancer mortality between population groups according to ethnicity and SES. Evidence shows, for men, at least, that people with lower SES have worse survival than those from higher SES (Scully and Bedi 2000, Conway et al 2007; Downer 2007).
In the USA survival rates from oral cancer among blacks have been lower than among whites (Scully and Bedi 2000; Morse and Kerr 2006; Shiboski et al. 2007), which has been due to lower SES, more advanced stage of disease, and differences in type of treatment they received (Scully and Bedi 2000). Difference in survival rate has also been reported among three major ethnic groups in Taiwan, which has mainly been attributed to the difference in their cultural, behavioural (betel quid-chewing habit) and socio-economic differences (Chen et al. 2007). Incidence rate and mortality from oral cancer has also been higher in American Hispanic men, from Puerto Rican origin (Cruz et al. 2006).

Some reports suggest that factors such as age, gender, and risk habits may have less or no relevance to the prognosis of oral cancer once the patients are treated (Ribeiro et al. 2000; Prieto et al. 2005). Comorbidity might be more important with regard to treatment selection and prognosis (Ribeiro et al. 2000).

2.4.1.2. Tumour-related factors

Clinical and pathological Tumour, Node, Metastasis (TNM) stage is an important and reliable predictor of survival (Chiesa et al. 1999). Details of TNM classification are in Table 2.2. Clinical T and N stage and the presence of extra-capsular spread have been reported as the most important risk factors for the development of distant metastasis in patients with oral SCC (Kowalski et al. 2005).
Table 2.2. TNM classification of oral cancers

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1N0M0</td>
</tr>
<tr>
<td>II</td>
<td>T2N0M0</td>
</tr>
<tr>
<td>III</td>
<td>T3N0M0</td>
</tr>
<tr>
<td></td>
<td>T1,T2 or T3N1M0</td>
</tr>
<tr>
<td>IV</td>
<td>Any T4, N2, N3 or M1</td>
</tr>
</tbody>
</table>

TNM clinical classification (Sobin and Wittekind 2002)

**T - Primary tumour**
- TX  Primary tumour can not be assessed
- T0  No evidence of primary tumour
- Tis Carcinoma in situ
- T1  Tumour 2 cm or less in greatest dimension
- T2  Tumour more than 2 cm but not more than 4 cm in greatest dimension
- T3  Tumour more than 4 cm in greatest dimension
- T4a (Lip) tumour invades through cortical bone, inferior alveolar nerve, floor of the mouth, or skin (chin or nose)
- T4a (Oral cavity) tumour invades through cortical bone, into deep/ extrinsic muscle of tongue, maxillary sinus, or skin of face
- T4b (Lip and oral cavity) tumour invades masticator space, pterygoid plates or skull base, or encases internal carotid artery

* Superficial erosion alone of bone/ tooth socket by gingival primary is not sufficient to Classify a tumour as T4.

**N - Regional lymph nodes**
- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
- N2 Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
- N2a Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
- N2b Metastasis in multiple ipsilateral lymph nodes, not more than 6 cm in greatest dimension
- N2c Metastasis in bilateral or contralateral lymph nodes, not more than 6 cm in greatest dimension
- N3 Metastasis in a lymph node more than 6 cm in greatest dimension

* The regional lymph nodes are the cervical lymph nodes. Midline nodes are considered ipsilateral nodes.

**M - Distant metastasis**
- MX Distant metastasis cannot be assessed
- M0 No distant metastasis
- M1 Distant metastasis
2.5. Treatment

2.5.1. Treatment modalities in oral cancer patients

The aim of treatment for oral cancer patients, as of any other cancer treatment, is to obtain the highest cure rate and the lowest morbidity with minimal side effects. Surgery and radiotherapy have been the mainstay of treatment for oral cancer. Surgery is the method of choice for both tumour resection and tissue reconstruction (Boyle 2001). The decision regarding treatment is influenced by several factors such as patient’s general health status (Ribeiro et al. 2000), TNM stage of tumour at the time of diagnosis (Marcus et al. 2004; Kowalski et al. 2005), tumour proximity to vital organs, clearance of surgical margins, and presence of osseous, neural, or vascular invasion (Woolgar et al. 1999).

2.5.2. Preserving QOL in oral cancer patients

Cancers of the OC are highly fatal, and both the disease and the treatment have serious morbid effects. All methods of treatment, surgery, radiotherapy, and chemotherapy, cause significant side effects, especially as usually they are used in combination, simultaneously or consecutively. Some of these effects are: pain, disfigurement (Wax et al. 1999; Knezevic et al. 2002), salivary dysfunction, mucositis, xerostomia (Parliament et al. 2004), swallowing disorders (Lazarus et al. 1996), osteoradionecrosis, and psychological problems (Hassanein et al. 2001). Of these adverse effects some are of short duration, but the others may persist for the patient’s lifetime. The QOL of oral cancer survivors therefore, is generally poor (Ship 2002).

Management of oral cancer patients include a multiphase and continuous team approach. The process needs collaboration among all specialists and health care workers involved in the patient’s therapy (Boyle 2001). It also requires continuous and effective communication among the patient and care providers (Hassanein et al. 2001). Patients should be educated about the risk factors and encouraged not to continue smoking and heavy drinking (Scully and Porter 2000). Therapy for salivary hypo-function or dysfunction, prevention of new and recurrent dental caries, dental prostheses, osseointegrated implants, and new surgical reconstructive techniques all help to preserve and improve QOL (Ship 2002). Oro-dental care should also be performed before starting any cancer therapy to prevent complications such as osteoradionecrosis (Scully and Felix
A more conservative bone resection can be considered as an option for preserving the continuity of the mandible and its function when a non-infiltrative or erosive pattern of mandibular invasion by a malignant oral tumour is evident (Brown et al. 2002).

2.6. Prevention

2.6.1. Primary prevention

The most important cause of preventable morbidity and mortality is tobacco use (Bsoul et al. 2005). It is estimated to account for about 41% of oral/pharyngeal cancer cases in men, and 11% in women (WHO 2005). A recent study suggests that tobacco cessation at the earliest possible time in life is the most significant public health measure to control oral cancer (Llwellyn et al. 2004).

Prevention activities focused on risk factors of oral cancer can be through existing oral health services or new community programmes targeted at different population groups (Petersen 2003b). Oral health care professionals especially dentists, should further investigate the patient’s family and social histories to elicit information about tobacco and alcohol use (Bsoul et al. 2005).

2.6.2. Secondary prevention

Thorough inspection of OC in high-risk individuals facilitates early diagnosis of potentially malignant lesions. However, the effectiveness of national organized screening in reducing incidence of and mortality from oral cancer remains to be established (Stewart and Kleihues 2003). Due to insufficient evidence on the costs, benefits, effectiveness, feasibility, and appropriateness of screening for oral cancer, such a programme could not be recommended (Daly et al. 2005). Thus, in the absence of science-based evidence for a national screening programme, thorough and detailed examination of the OC and head and neck region should be implemented during dental check-ups (Silverman 2001). This examination composes the visual assessment and manual palpation of extra-oral head and neck areas, intraoral soft tissues, and dental and periodontal tissues (Bsoul et al. 2005).
3. AIMS OF THE STUDY

3.1. General aim

The general aim of the present study was to investigate the burden of oral cancers in Tehran, Iran.

3.2. Specific objectives

To achieve this aim, the following specific objectives were set:

1. To determine the patient and tumour characteristics of oral cancers in Tehran, Iran
2. To evaluate survival rates in patients with OC cancer
3. To evaluate survival rates in patients with lip cancer
4. To evaluate the delay in diagnosis of OC cancer

3.3. Hypotheses

Working hypotheses: a) Most oral cancer patients in Tehran, Iran, have advanced tumours at the time of diagnosis. b) Survival rates between oral cancer patients in early and late tumour stages significantly differ. c) The difference between survival rates in these patients is due to the delay in diagnosis.
4. MATERIALS AND METHODS

4.1. Study background

According to the 2003 report of the IMOHME, based on the data from 70% of the country’s pathology centres and hospitals, oropharyngeal cancers accounted for 3% of all cancers in Iran. There existed no population based cancer registry in Iran during the study period, which made it impossible for us to provide a reliable incidence or prevalence rate. To the researcher’s knowledge, no research reports are available regarding oral cancers in Tehran, Iran.

4.2. Study population

The target population of this study comprised three groups: 1) a retrospective cohort of oral cancer patients attending 30 hospitals in Tehran, Iran during 1993-2003 (n=1042), 2) a retrospective cohort of OC (n=470) and lip (n=82) cancer patients attending five university hospitals in Tehran, Iran, during 1996-2003, and 3) consecutive OC cancer patients attending three main university hospitals in Tehran during September 2004 to September 2006 (n=100).

4.3. Pilot study

A pilot study was performed in two stages, to revise the contents of the data collection form and the study questionnaire and to test the feasibility of the study method. In order to revise the contents of the primary data collection form, a study was conducted by reviewing 50 head and neck cancer patients’ records in three hospitals. Another study was performed in the second stage with ten head and neck cancer patients other than OC cancer patients, such as those with cancer of the larynx to revise the primary questionnaire.
4.4. Data collection

**Patient and tumour characteristics:** For determining the characteristics of malignant oral tumours, data were obtained from patient records of 1042 patients diagnosed with invasive oral cancers during 1993-2003 in 30 major hospitals in Tehran. Primary tumour sites were recorded according to the 10th revision of the International Classification of Disease coding system (WHO 2003) using ICD codes from C00 to C10. This classification is shown in Table 4.1. In this study, oral cancers on the lip, tongue, gum, FOM, other sites in the mouth (including buccal mucosa, labial mucosa, palatal mucosa, retro-molar area, and unspecified areas), tonsil, oropharynx and major salivary glands were included. Data were analysed in three groups according to tumour aetio-pathological similarities: tumours of the lips (C00), of the OC (C01-C06; C09-C10), and of major salivary glands (C07-C08).

**Survival rate:** To evaluate the survival rates in oral cancer patients the study included a retrospective cohort of 470 primary OC and 82 lip cancer patients diagnosed at five university hospitals in Tehran in 1996-2003.

**Diagnostic delay:** To assess delay in diagnosis, 100 patients with primary OC SCC (ICD-10 sites C01-C06) (WHO 2003), consecutively referred to three university hospitals in Tehran during September 2004 to September 2006, were studied.
Table 4.1. Primary tumours’ anatomical sites

**Malignant neoplasms of lip (C00)**
1. External upper lip (vermilion border)
2. External lower lip (vermilion border)
3. Commisures
4. Mucosa of upper and lower lips (buccal or oral aspects of lips)

**Malignant neoplasms of oral cavity and oropharynx (C01-C06, C09-C10)**
1. Tongue (C01-C02)
   a. Base of tongue posterior to the vallate papilla (posterior third)
   b. Dorsal surface and lateral borders anterior to vallate papilla (anterior two-thirds)
   c. Anterior ventral surface, fraenulum linguae
   d. Lingual tonsil
2. Upper alveolus and gingiva (upper gum) (C03)
3. Lower alveolus and gingiva (lower gum) (C03)
4. Floor of the mouth (C04)
5. Hard and soft palate, uvula (C05)
6. Buccal mucosa (C06)
   a. cheek mucosa
   b. retro molar areas
   c. upper and lower buccal/ labial sulci (vestibule of the mouth)
   d. minor salivary glands
7. Tonsil, tonsillar fossa, tonsillar pillars (C09)
8. Valleecula, anterior surface of epiglottis, oropharynx (C10)

**Malignant neoplasms of major salivary glands (C07-C08)**
1. Parotid gland (C07)
2. Submandibular gland, Sublingual gland (C08)

---

1 Modified from International Classification of Diseases (ICD), ICD-10 (WHO 2003)

### 4.5. Theoretical model of the study

The theoretical concept of the study is shown in **Figure 4.1**. According to this model, incidence, survival (mortality) rate, health-related QOL, and financial burden are the four main components of the total burden of oral cancer. By putting the patient and tumour characteristics and tumour detection in associations with the disease burden, this model assumes that it is possible to modify the burden by changing the related factors. This would be the basis for primary (targeting risk behaviours) and secondary prevention (early detection and reduction of diagnostic delay) of oral cancers. The present study’s focus was
on the epidemiologic part of the oral cancer burden, i.e., patient and tumour characteristics, survival rate, and diagnostic delay.

**Fig. 4.1.** Theoretical model of the study

![Theoretical model of the study](image)

### 4.6. Questions and variables

#### 4.6.1. Patient characteristics

The data collection form included sections for personal data such as patient’s age at time of diagnosis, gender, and place of residence.

#### 4.6.2. Tumour characteristics

Tumour characteristics included in the data collection form were histo-pathological type, primary tumour anatomical site, and tumour stage at diagnosis. TNM staging of tumours
was according to clinical staging (Sobin and Wittekind 2002) based on T (tumour size, at the largest diameter) N (nodal involvement), and M (metastasis) status as recorded in the patient files.

4.6.3. Survival

For survival analysis, the patients were followed from the date of diagnosis to late 2005. We defined survival as the time from diagnosis until December 31, 2005 or until death due to oral cancer, whichever occurred first. Vital status was ascertained through a combination of information from patient records, telephone calls, and the death-register files at the IMOHME. Information abstracted from patient records included birth year, gender, date of diagnosis; TNM stage, primary tumour site, and histopathology type. Treatment modality (surgery, pre- or postoperative radiotherapy, chemotherapy) and the final admittance dates to the hospital were also recorded, as were the date and the cancer or non-cancer causes of death.

4.6.4. Diagnostic delay

Data were obtained by means of structured questionnaire-interviews that inquired about patient demographics such as gender, age, marital status, and place of residence, smoking history, dental visits, the initial source of referral to the centre, date of onset of symptoms, and date of consulting the first professional. The medical record of each patient was reviewed to retrieve information on date of diagnosis, primary tumour site, and TNM stage of tumour at diagnosis. Diagnostic delay was defined as the period from onset of symptoms to the final diagnosis of oral cancer (McLeod et al. 2005). This period was divided into two phases: 1) time from onset of symptoms to patient’s first professional visit (patient delay) and 2) time from the first professional visit to the final diagnosis (professional delay). Interviews were performed before the beginning of any cancer therapy.

4.7. Statistical methods

Chi-square, t-test, and ANOVA served to test for needed statistical significance between subgroups for mean values and frequencies. Regression models were applied to determine the extent to which the factors were able to explain variation in the data. The terms of the models facilitated the calculation of the corresponding ORs and their 95% confidence intervals (CI). Survival curves were generated by Kaplan-Maier methods. The relationships between survival status and other study factors were evaluated by the log-rank test. For further survival analysis Cox’s regression model was adopted to calculate the hazard ratios.
5. RESULTS

5.1. What are the patient and tumour characteristics of oral cancers in Iran (I)?

Oral cancers were studied separately in three groups: OC, lip, and salivary glands. OC tumours were more frequent (65%). The majority of all cancer patients were men (59%) and in the 41-64 age group (43%). The mean age of the patients was 61.2 (SD 15, median 64, range 14-103), 58.7 (SD 14, median 62, range 27-87), and 51.5 (SD 17, median 52, range 6-85) for OC, lip, and salivary gland cancers, respectively ($P < 0.001$). A clear gender and age difference emerged between patients with these tumours ($P < 0.001$). Males dominated, especially in lip cancers (85%), and the majority of the patients in all these three groups were over 40 (Table 5.1). Further analyses showed no gender difference by age within these three tumour sites (Figure 5.1). Tongue cancers were the most prevalent OC type (50%). No age and gender difference appeared among OC subsites (Table 5.2).

Table 5.1. Primary tumour site in oral cancer patients (n = 1042) by gender and age

<table>
<thead>
<tr>
<th>Variable</th>
<th>Oral cavity</th>
<th>Lip</th>
<th>Salivary glands</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (%)</td>
<td>No (%)</td>
<td>No (%)</td>
<td>No (%)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>426 (41)</td>
<td>319 (47)</td>
<td>22 (15)</td>
<td>85 (38)</td>
</tr>
<tr>
<td>Male</td>
<td>616 (59)</td>
<td>356 (53)</td>
<td>124 (85)</td>
<td>136 (62)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 40</td>
<td>152 (15)</td>
<td>76 (11)</td>
<td>19 (13)</td>
<td>57 (26)</td>
</tr>
<tr>
<td>41-64</td>
<td>449 (43)</td>
<td>277 (41)</td>
<td>69 (47)</td>
<td>103 (47)</td>
</tr>
<tr>
<td>65 or more</td>
<td>441 (42)</td>
<td>322 (48)</td>
<td>58 (40)</td>
<td>61 (27)</td>
</tr>
<tr>
<td>Total</td>
<td>1042 (100)</td>
<td>675 (100)</td>
<td>146 (100)</td>
<td>221 (100)</td>
</tr>
</tbody>
</table>
Fig. 5.1. Distribution (%) of oral cancer patients (n = 1042) by age, men and women separately, for three tumour sites (no gender difference by age within sites)

Table 5.2. Primary tumour site in oral cavity cancer patients (n = 675) by gender and age
Most of the OC cancer patients (59%) were in advanced stages (stages III or IV) at diagnosis, whereas 29% of lip cancers were diagnosed in late stages (Table 5.3). Data regarding TNM staging were missing from patient records in 15% of cases.

Regarding the histological type of tumours 87% of OC cancers were SCC; this figure was 95% for lip cancers. Salivary gland tumours were mostly mucoepidermoid carcinomas (28%). For all the three sites the occurrence of SCCs increased at successively older ages. Of all histological types, SCCs comprised 48%, 72%, and 81% in patients aged 40 and younger, 41 to 64, and those aged 65 and older, ($P < 0.001$).

**Table 5.3.** Stage of tumours at diagnosis in oral cancer patients (n = 882) by gender, age, and primary tumour site.

<table>
<thead>
<tr>
<th>Variable</th>
<th>No (%)</th>
<th>I or II</th>
<th>III or IV</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No (%)</td>
<td>No (%)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>370 (42)</td>
<td>172 (43)</td>
<td>198 (41)</td>
<td>0.23</td>
</tr>
<tr>
<td>Male</td>
<td>512 (58)</td>
<td>224 (57)</td>
<td>288 (59)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 40</td>
<td>125 (14)</td>
<td>51 (13)</td>
<td>74 (15)</td>
<td>0.60</td>
</tr>
<tr>
<td>41-64</td>
<td>382 (43)</td>
<td>175 (44)</td>
<td>207 (43)</td>
<td></td>
</tr>
<tr>
<td>65 or more</td>
<td>375 (43)</td>
<td>170 (43)</td>
<td>205 (42)</td>
<td></td>
</tr>
<tr>
<td>Tumour site</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral cavity</td>
<td>578 (66)</td>
<td>237 (60)</td>
<td>341 (70)</td>
<td></td>
</tr>
<tr>
<td>Lip</td>
<td>121 (14)</td>
<td>86 (22)</td>
<td>35 (7)</td>
<td>0.00</td>
</tr>
<tr>
<td>Salivary gland</td>
<td>183 (20)</td>
<td>73 (18)</td>
<td>110 (23)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>882 (100)</td>
<td>396 (100)</td>
<td>486 (100)</td>
<td></td>
</tr>
</tbody>
</table>
5.2. How long is the survival of oral cancer patients in Iran after diagnosis (II, III)?

**Oral cavity cancer patients’ survival:**
The overall 5-year survival of the OC cancer patients was 30%. For the survival analysis, these patients were followed for a maximum of 116 months (mean (SD) 32 (26), range 0-116). Of all 470 patients, 335 (71%) died of their oral cancer, 18 patients (4%) died of other causes, 80 (17%) survived, and 37 (8%) were lost to follow-up. No associations emerged between gender and age and patient survival. However, stage of tumour at diagnosis and treatment were related to survival. Patients diagnosed at stages III or IV had shorter survival than those diagnosed at stages I or II ($P < 0.05$) (Figure 5.2). The outlook was also poor for patients treated with radiotherapy alone; they were more likely to die sooner ($P < 0.05$). No difference existed in patient survival according to histological type of tumour (Table 5.4).

**Fig. 5.3.** Survival rate in oral cavity cancer patients ($n = 470$) by stage of tumour at diagnosis
Further analysis by Cox’s multivariate method showed that stage of tumour at the time of diagnosis and treatment were the most important determinants of survival compared with age, gender, and histological type of OC tumour (Table 5.4). Overall survival was longer for patients with cancer in stages I or II than for those with stages III or IV (OR = 3, 95% CI = 2.2-4.2). Longer survival was evident for patients treated with surgery than for those who had undergone surgery together with radiotherapy, or radiotherapy alone (OR = 2.8, 95% CI = 1.7-4.5).

Table 5.4. Five-year survival rates for OC (n = 470) and lip cancer (n = 82) patients by age, gender, stage of tumour at diagnosis, treatment, and histological type.

<table>
<thead>
<tr>
<th>Variable</th>
<th>No (%)</th>
<th>Oral cavity</th>
<th>Lip</th>
<th>P-value</th>
<th>Oral cavity</th>
<th>Lip</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>213 (45)</td>
<td>12 (15)</td>
<td>(25)</td>
<td>*</td>
<td>0.68</td>
<td>0.32</td>
</tr>
<tr>
<td>Male</td>
<td>257 (55)</td>
<td>70 (85)</td>
<td>(31)</td>
<td>(65)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 40</td>
<td>57 (12)</td>
<td>13 (16)</td>
<td>(33)</td>
<td>(36)</td>
<td>0.33</td>
<td>0.35</td>
</tr>
<tr>
<td>41-64</td>
<td>193 (41)</td>
<td>35 (43)</td>
<td>(32)</td>
<td>(66)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>65 or more</td>
<td>220 (47)</td>
<td>34 (41)</td>
<td>(25)</td>
<td>(65)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stage of tumour</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>92 (20)</td>
<td>35 (43)</td>
<td>(51)</td>
<td>(81)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>73 (16)</td>
<td>17 (21)</td>
<td>(44)</td>
<td>(75)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>70 (15)</td>
<td>11 (13)</td>
<td>(13)</td>
<td>(45)</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>IV</td>
<td>167 (35)</td>
<td>9 (11)</td>
<td>(12)</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>68 (14)</td>
<td>10 (12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>70 (15)</td>
<td>34 (42)</td>
<td>(54)</td>
<td>(69)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery + radiotherapy</td>
<td>274 (58)</td>
<td>35 (43)</td>
<td>(27)</td>
<td>(75)</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>72 (15)</td>
<td>6 (7)</td>
<td>(08)</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>54 (12)</td>
<td>7 (8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCC</td>
<td>404 (86)</td>
<td>77 (94)</td>
<td>(29)</td>
<td>(62)</td>
<td>0.47</td>
<td>0.62</td>
</tr>
<tr>
<td>Non-SCC</td>
<td>66 (14)</td>
<td>5 (6)</td>
<td>(33)</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>470 (100)</td>
<td>82 (100)</td>
<td>(30)</td>
<td>(62)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Kaplan-Maier analysis  b log-rank test  c Scuamous cell carcinoma * not estimated due to small n.
Lip cancer patients’ survival:
The overall five-year survival rate of the lip cancer patients was 62%. Gender, age, and histological type were not associated with survival. Treatment modality and stage of tumour at diagnosis were related to survival (Table 5.4.). Patients treated with surgery were more likely to have a longer survival ($P < 0.05$). Patients diagnosed at stages III or IV had a dismal prognosis and lower survival rates ($P < 0.05$) (Figure 5.3).

Fig. 5.3. Survival rate in lip cancer patients ($n = 82$) by stage of tumour at diagnosis

The multivariate analysis using Cox’s regression method showed that treatment modality and stage of tumour were the most important determinants of lip cancer patients’ survival (Table 5.5.). The overall survival was longer for patients diagnosed at early stages than in those diagnosed at stages III or IV (OR = 3, 95% CI = 1.1-7.9). Patients treated with radiotherapy alone had lower survival rates than did those who had undergone the other treatment methods (OR = 7.7, 95% CI = 1.3-39.7).
**Table 5.5.** Determinants of length of survival assessed by Cox’s regression analysis in patients with cancer of the OC (n = 470) and lip (n = 82).

<table>
<thead>
<tr>
<th>Variable</th>
<th>ES (^1)</th>
<th>SE (^2)</th>
<th>OR (^3)</th>
<th>95% CI (^4)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td>OC Lip</td>
<td>OC Lip</td>
<td>OC Lip</td>
<td>OC Lip</td>
<td></td>
</tr>
<tr>
<td>(Male (^a), female)</td>
<td>0.2 0.5</td>
<td>0.1 0.6</td>
<td>1.2 1.6</td>
<td>0.9-1.6</td>
<td>0.5-5.2</td>
</tr>
<tr>
<td><strong>Age group (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 40 (^a)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>41-64</td>
<td>0.4 1.1</td>
<td>0.2 0.8</td>
<td>1.5 3.0</td>
<td>0.9-2.3</td>
<td>0.7-13.9</td>
</tr>
<tr>
<td>65 or more</td>
<td>0.4 0.7</td>
<td>0.2 0.7</td>
<td>1.5 2.0</td>
<td>1.0-2.3</td>
<td>0.5-7.9</td>
</tr>
<tr>
<td><strong>Stage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(I or II (^a), III or IV)</td>
<td>1.1 1.0</td>
<td>0.1 0.5</td>
<td>3.0 3.0</td>
<td>2.2-4.2</td>
<td>1.1-7.9</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery (^a)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery + radiotherapy</td>
<td>0.7 0.1</td>
<td>0.2 0.5</td>
<td>1.1 1.1</td>
<td>0.7-1.6</td>
<td>0.4-3.1</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>1.0 2.0</td>
<td>0.2 0.8</td>
<td>2.8 7.7</td>
<td>1.7-4.5</td>
<td>1.3-39.7</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(SCC (^6), non-SCC)</td>
<td>0.1 1.0</td>
<td>0.2 0.9</td>
<td>1.1 2.9</td>
<td>0.7-1.5</td>
<td>0.5-16.1</td>
</tr>
</tbody>
</table>

\(^1\) Estimate of strength \(^2\) Standard error \(^3\) Odds ratio \(^4\) Confidence interval \(^5\) Oral cavity
\(^6\) Squamous cell carcinoma \(^a\) reference category
5.3. How much time elapses between symptoms’ notice by patients and diagnosis of oral cancers in Iran (IV)?

The time elapsed between oral cancer patients’ first notice of the symptoms and definite diagnosis, i.e., the diagnostic delay, ranged from 1 to 36 months, with a mean of 7.2 months (SD 7.5, median 4). The mean patient and professional delays were 5.3 months (SD 6.1, median 2) and 2.1 months (SD 2.1, median 1), respectively. Mean delays by age, gender, marital status, place of residence, tumour site, stage of tumour, smoking history, referral source, and dental visit are shown in Figure 5.2.

Marital status, stage of tumour at diagnosis and occurrence of dental visit within the past 12 months were associated with diagnostic delay ($P < 0.05$). Patients living without a spouse, those diagnosed with an advanced-stage tumour, and patients with no dental visits within the past 12 months were more likely to have longer diagnostic delays. Logistic regression analyses revealed that the most important determinants of a diagnostic delay of more than four months were being single (OR = 4.8; 95% CI 1.5-14.8; $P < 0.05$) and being at advanced stages of disease at the time of diagnosis (OR = 5.2; 95% CI 1.8-15.6; $P<0.01$).

Patients with advanced tumour stages were more likely to have longer patient delay than those at early stages (OR = 5.6; 95% CI 1.8–17.3; $P < 0.05$), as were patients living alone (OR = 7.1; 95% CI 2.0–24.7; $P < 0.05$). Logistic regression analysis revealed that advanced stage of tumour at diagnosis (OR = 3.4; 95% CI 1.2–9.4; $P < 0.05$) and living alone (OR = 3.5; 95% CI 1.2–10.3; $P < 0.05$) were determinants of professional delays of more than one month.
Fig. 5.2. Mean patient, professional, and diagnostic delay in oral cavity cancer patients (n=100), by different factors.
6. DISCUSSION

6.1. Methodological considerations

The present study investigated patient and tumour characteristics of oral cancers in Tehran, Iran, during a ten-year period from 1993 to 2003, with the main focus on OC cancers. The study further evaluated survival rates and the time elapsed between symptoms being noticed by oral cancer patients and the diagnosis. A nation-wide population-based cancer registry in Iran began in 2003; therefore we used hospital-based data in order to have a general preview of oral cancers in Tehran.

Of the more than 100 hospitals in Tehran, 30 hospitals are involved in oral cancer treatment. All the university, military, and main private hospitals, in addition to the Cancer Institute of Iran, provided data for the study. The Cancer Institute of Iran was established in 1955 by the National Red Cross Foundation as the first comprehensive cancer centre in Iran, providing diverse programmes in prevention, early detection, patient care, education, community activities, and international collaboration.

Although the patients studied came from 30 major hospitals in Tehran, the lack of a nation-wide population-based cancer registry until 2003 makes it difficult to give exact prevalence or incidence values for oral cancers. Therefore for the period 1993 to 2003, we evaluated the patient and tumour characteristics for oral cancers.

All eligible patients were identified from the patient attendance list and information files held in the records department of each hospital. No patient can be admitted to a hospital or treated without first filling in the required forms and documents. Study data collection forms and records files were cross-checked to ensure inclusion of all eligible cases.

For the survival analysis of oral cancer patients, vital status was ascertained through a combination of information from patient records, telephone calls, and death register files at the Iran Ministry of Health. To evaluate the time elapsed from patient noticing of symptoms and the diagnosis of oral cancer, all the information gathered during the
interviews and all the patients’ responses were validated by referring to and checking them with their medical records at the hospital, or at the physician’s or dentist’s office.

6.2. Results of the study

6.2.1. Patient and tumour characteristics

Oral cancer has traditionally been a disease dominated by the male gender (Moore et al. 2000; Silverman 2001; Stewart and Kleihues 2003). Higher alcohol and tobacco use and outdoor occupations in men have been considered the main reasons for the male predominance, whereas recent reports from different parts of the world show a decreasing male to female ratio among OC cancer patients (Luukkaa et al. 2003; Tarvainen et al. 2004; Rautava et al. 2007). This has been attributable to an increase in smoking among women, particularly in western countries. In the present study, oral cancer occurred more frequently in men, with a male to female ratio of 1.4:1. Smoking prevalence is estimated as 20 to 26% among Iranian males and 2 to 4% among females (Mosavi-Jarahi et al. 2004). This may be a plausible reason for the higher occurrence of oral cancers in Iranian men.

Similar to the vast majority of the previous reports from all over the world (Moore et al. 2000; Parkin et al. 2002, Silverman 2003) only a small proportion of OC tumours were in patients aged 40 and younger, average age at the time of diagnosis was 61, and SCC was the most frequent histological type of OC and lip cancers. Among all OC cancers, the tongue was the most common site of occurrence, in accordance with that reported from different parts of the world, mostly western counties such as the UK (Moore et al. 2000). Oral SCC is amenable to early detection and clearly attributable to lifestyles, smoking, and alcohol drinking, so it is usually regarded as preventable. Although SCC is the most prevalent type of malignant oral tumours, each distinct histological type needs to be considered according to the individual prognosis in patient management and treatment.

Almost 60% of the OC cancer patients were at stage III or IV at diagnosis. Late diagnosis of oral cancers generally results in a very poor prognosis and strongly reduced survival rates. Oral cancer treatment in advanced stages means radical surgical resection and comprises complicated post-operative reconstructive procedures. Furthermore, surgery
should be accompanied by radiotherapy and sometimes chemotherapy. The present results speak for the necessity of a national programme underscoring early detection of oral cancer.

6.2.2. Survival

Oral cavity cancer:
The overall survival outcome for oral cancer is dismal, with the 5-year survival being around 50%. The 5-year survival in the present study is comparable with that reported from developing countries. Further analysis showed that OC cancer patients with stage I or II tumours had the longest survival, while the lowest was in later stages. This reveals the smaller influence of treatment when tumours have been diagnosed in advanced stages.

Patients treated with radiotherapy alone had shorter survival than those who were treated surgically or who had been operated on and had had adjuvant radiotherapy. Of all patients who had radiotherapy as the sole treatment modality, 71% were at an advanced disease stage at the time of diagnosis and were plausibly in poor general health. These findings support earlier reports regarding the relation between treatment and survival in patients with OC cancer (Chen et al. 1999; Carvalho et al. 2004; Chen et al. 2004).

Primary surgical management with adjuvant radiotherapy has been associated with high rates of local control in previous reports (Chen et al. 1999; Woolgar et al. 1999; Davidson et al. 2001; Carvalho et al. 2004). However, the reason for longer survival found here for patients treated by operation alone may be mainly that this method is used for treatment of earlier tumours.

The decision to treat is based not only on the stage of tumour but also on several other factors such as the general health of the patient, state of surgical margins, and in some instance by the patient’s decision about treatment. These all may have an impact on the outcome of the treatment and on survival.
**Lip cancer:**

Lip cancer is a form of oral cancer but has a distinct epidemiology and different tumour behaviour (Moore et al. 1999). Although this cancer is not common in Asia, in contrast to other oral cancers which are prevalent in southern parts of this continent, more thorough assessments are needed, since lip cancer is usually considered to be easily detectable and thus curable (Zitsch et al. 1995; de Visscher et al. 1999).

In the present study, lip cancer patients’ overall survival rates for 1, 2, and 5 years after diagnosis were 91%, 86%, and 62%. These figures are lower than those reported from western countries. One possible reason may be delay in treatment which leads to the much higher percentage of advanced SCCs at the time of treatment and thus lower survival of lip cancer patients.

It was found that malignant lip tumours occurred mostly in men, on the lower lip, and as SCCs. The findings revealed that gender, age, and histological type of tumours were insignificant predictors of survival, both in univariate and multivariable analyses. The results regarding the relationship of lip cancer patients’ survival with gender, age, tumour stage, treatment modality, and histo-pathological type were in line with previous results (Moore et al. 1999; de Visscher et al. 1999; Boyle 2001; Babington et al. 2003). Survival was higher in patients diagnosed at earlier tumour stages. Many previous reports also show higher survival rates for patients diagnosed at stages I or II (de Visscher et al. 1999; McCombe et al. 2000; Babington et al. 2003; Vartanian et al. 2004).

In the present study, further analyses showed that patients treated with radiotherapy alone had lower survival rates than those who had undergone surgery together with or without adjuvant radiotherapy. These findings support previous studies which show higher rates of recurrence and lower disease-free survival in lip cancer patients initially treated with radiotherapy (de Visscher et al. 1999, Zitsch et al. 1999).
6.2.3. Delay in diagnosis

Early diagnosis of oral cancers leads to higher survival rates and better quality of life outcomes (Kowalski et al. 1994; Onizawa et al. 2003). In the present study the mean patient, professional, and diagnostic delays were higher than those reported from other, especially developed, countries (Dimitroulis et al. 1992; Jovanovic et al. 1992; Rubright et al. 1996; Kerdpon and Sriplung 2001a; Pitiphat et al. 2002). No national programme exists for the prevention of oral cancers in Iran which may explain these findings.

This study mainly shows that the “patient delay” constitutes a substantial part of the total delay time elapsed between the onset of symptoms and diagnosis. Such finding is in agreement with those reported by other investigators (Kowalski and Carvalho 2001; Hollows et al 2000; Kerdpon and Sriplung 2001a and b; Onizawa et al. 2003; Brouha et al. 2005). As the majority of oral cancer patients in the present study had advanced-stage tumours at diagnosis, patient delay in seeking medical attention may be a contributing cause in a considerable number of OC cancer patients’ deaths.

Although the time period from patients’ first awareness of symptoms to the first professional visit is called the “patient delay”, patient is not the only one responsible. Other factors such as access to health care services contribute to the length of this time (Diz Dios et al. 2005). Oral cancer patients may have insufficient or incorrect knowledge to appropriately interpret the relevance of their symptoms to a malignancy, and they may consider the symptoms to be non-serious or harmless (De Nooijer et al. 2001; Scott et al. 2006) or possibly fail to seek help due to fear of cancer or lack of faith in medical treatment (De Nooijer et al. 2001). Psychological factors such as distress and coping styles, as well as socio-economic factors have been shown to affect patients’ health-seeking behaviours (Tromp et al. 2004; Tromp et al. 2005a; Scott et al. 2006).

The present findings reveal that patients living alone had greater tendencies for longer patient and, surprisingly, professional delays. Married patients may have better health habits and mutual support and indeed seek medical care with less delay (Scott et al. 2005), which may be mainly due to the supportive and motivational role of their partners (Tromp et al. 2004). Another plausible explanation for this finding is the lack of comprehensive and socially supportive health care for cancer patients in Iran.
Previous studies have reported different results regarding the association between an advanced stage of disease at the time of diagnosis and delay in diagnosis (Carvalho et al. 2002; Pitiphat et al. 2002; Onizawa et al. 2003; Ho et al. 2004; McGurk et al. 2005; McLeod et al. 2005; Scott et al. 2005). In the present study, as in some others (Kerdpon and Sriplung 2001a and b; Pitiphat et al. 2002; Onizawa et al. 2003), an advanced stage of tumour was associated with a longer diagnostic delay as well as with its two components: patient and professional delay.

Three major hypotheses may explain the controversies regarding the association between tumor stage and diagnostic delay: 1) the “tumor biology” or “tumor aggressiveness” hypothesis: patients with slow-growing tumors may experience longer diagnostic delay, however, they are more likely to be diagnosed with an early stage tumor than patients with fast-growing tumors, 2) the “misdiagnosis” or “silent tumor” hypothesis: patients with silent oral tumors may notice the minor changes early and consult a doctor (short patient delay), but the professional misdiagnoses the lesion as benign (long professional delay) which leads to an advanced stage tumor at the time of diagnosis (Carvalho et al. 2002; Scott et al. 2005), and 3) “logical” hypothesis. Our findings favor the “logical” hypothesis, which suggests that a longer diagnostic delay (both patient and professional) is related to an advanced tumor stage at the time of diagnosis (Carvalho et al. 2002).

Findings of the present study show that not having visited a dentist within the past 12 months was a significant determinant of patient delay. Patients who do not regularly visit a dentist seemed more likely to neglect their cancer-related symptoms or to misinterpret them as common oro-dental problems. One recent study (Bayat et al. 2006) revealed that 52% of Iranian adults aged 18 years or more had visited a dentist within the past 12 months, whereas only 16% of our patients reported having a dental visit within this period.
7. CONCLUSIONS

The specific conclusions of the study are:

1. Among all 1042 oral cancer patients’ records studied, OC tumours were most frequent. The majority of all cancer patients were men and in the 41-64 age group. Most OC cancer patients were at advanced stages at the time of diagnosis.
2. The overall five-year survival rate of patients with OC cancer was 30%. Survival was negatively related to stage of tumour at the time of diagnosis.
3. The overall five-year survival rate of patients with lip cancer was 62%. The survival was higher in patients diagnosed at earlier tumour stages than in those diagnosed at advanced stages.
4. The mean diagnostic delay found in this study was 7.2 months (SD 7.5), and “patient delay” constitutes a substantial part of the total time elapsed between the onset of symptoms and diagnosis.

8. RECOMMENDATIONS

The current study provides, for the first time, data as a baseline for interventions regarding the prevention of oral cancer in Iran. Considering possible future trends in the important risk factors such as smoking and chronic sun exposure in Iranian society, the data reported here are fundamentally important for use as a baseline for comparing any changes in oral cancer burden in terms of patient and tumour characteristics, survival rates, and diagnostic delay. This will help health care providers to organize an oral cancer prevention programme in Iran.

Based on the findings of this study, developing preventive programmes that focus on raising public awareness of the signs and symptoms of oral cancer is essential to promoting earlier diagnosis and treatment in Iran. In addition to people’s need for knowledge about oral cancer, they should be encouraged to be more conscious of any changes in the mouth which may develop into a malignancy.
Health care professionals, especially dentists and oral hygienists, should also be empowered to ensure that many potentially malignant and malignant lesions are recognized early and accurately. There is a clear need, in this regard, for additional training and for greater vigilance by the health work-force. Ongoing continuing education (CE) programmes for health care professionals, comprising theoretical and hands-on courses regarding oral cancer prevention and early detection, are greatly needed. The present study also speaks for more emphasis on oral cancer prevention and early detection in undergraduate medical and dental education.

Topics of CE courses cover various dental and medical subjects, so oral cancer prevention and early detection can be easily emphasized in CE courses using the existing structure of education for health care professionals in Iran. Oral cancer prevention should also be highlighted in congresses and seminars to present and discuss the latest concepts. If successful, these programmes could lead to faster diagnosis and better treatment outcomes for oral cancer patients.

In order to reduce the burden of oral cancer on the community recommended policies at the national administrative level are empowering the newly established nationwide population-based cancer registry, conducting interventions at community level to increase public awareness of the importance of early detection of oral cancers, removal of barriers to health-care system utilization by oral cancer patients, and mandating training programmes for health care professionals and encouraging comprehensive oral examination and patient-tailored risk counselling especially by dentists. An oral cancer prevention programme can be added to other cancer prevention programmes, especially cancers that share the common risk factors, such as pulmonary and oesophageal cancers. Further population-based studies on oral cancers and advances in their risk assessment, in surveillance and prevention, as well as evaluating patient-related QOL, and the financial burden of disease will be crucial for controlling the substantial threat of these cancers to public health.
9. SUMMARY

Although of low frequency in most countries, oral cancer is highly fatal, especially in advanced tumour stages. Despite many advances in treatment and rehabilitation techniques, there has been no improvement in the survival of oral cancer patients for decades, worldwide. This alarming indicator of disease burden highlights the importance of implementing preventive strategies focusing on early detection of malignant lesions, which requires the active contribution of the medical and dental work force. Because of their intimate knowledge of the oral cavity (OC), dentists are uniquely positioned to examine their patients for indications of developing oral cancer, and to counsel them about the oral health consequences of tobacco and alcohol use as the leading risk factors for oral cancer.

The present study, which was done for the first time, assessed the burden of oral cancer in Tehran, Iran, in terms of patient and tumour characteristics, survival and delay in diagnosis. The working hypothesis was that most oral cancer patients in Iran have advanced tumours at the time of diagnosis and that survival rates between oral cancer patients in early and late tumour stages significantly differ, which may be due to the delay in diagnosis.

Major referral hospitals (n=30) in Tehran, were selected, and patient records of 1042 patients diagnosed with invasive oral cancers during 1993-2003 were reviewed. Data were analysed in three groups according to primary tumour site: tumours of the lips, OC, and major salivary glands. For survival analysis, 470 patients with OC and 82 patients with lip cancers were followed from the date of diagnosis to late 2005. To assess the time elapsed between the presentation of symptoms and the final diagnosis, i.e., diagnostic delay, 100 patients with primary OC squamous cell carcinoma (SCC), consecutively referred to three university hospitals in Tehran during September 2004 to September 2006, were separately studied.

A data collection form and a questionnaire were designed and piloted to inquire about patient demographics, smoking history, dental visits, the initial source of referral to the
centre, date of onset of symptoms, and date of consulting the first professional. The medical record of each patient was reviewed to retrieve information on the date of diagnosis, primary tumour site, and TNM stage of tumour at the time of diagnosis. TNM staging was according to clinical staging based on T (tumour size, at the largest diameter) N (nodal involvement), and M (metastasis) status as recorded in the patient files. Questionnaire-interviews were performed for the 100 consecutive patients before the beginning of any cancer therapy. Diagnostic delay was divided into two phases: 1) time from onset of symptoms to patient’s first professional visit (patient delay) and 2) time from first professional visit to final diagnosis (professional delay).

The results showed that the majority of the OC cancer patients were at advanced tumour stages at the time of diagnosis. The overall five-year survival rate was 30% and 62% for OC and lip cancer patients, which is low particularly as compared to the rates reported from developed countries. Patients who were at stages III or IV at diagnosis had the lowest survival rate. The mean “diagnostic delay”, i.e., time elapsed from patient’s first noticing symptoms and the definite diagnosis, was longer (mean 7.2 months, SD 7.5), than that reported from many other countries and the “patient delay” constituted the substantial part of the total diagnostic delay.

In general it can be concluded that based on the present results, public awareness about the signs and symptoms of oral cancer should be increased. An improvement in the preventive orientation of all health care providers, especially dentists, is also required, which can come through emphasizing routine and thorough examination of the OC and head and neck region and early detection of potentially malignant and malignant lesions. Providing dentists, oral hygienists, and medical doctors with the opportunity to attend continuing education courses, seminars, and congresses on prevention of oral cancer will be helpful in this regard. Oral cancer prevention and early detection, as well as related public and health care provider education, are significant public health concerns that require increased and sustained attention in both the health care and policy systems.
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This thesis I dedicate to all the people of my country for their healthier future.

Katayoun Sargeran
Helsinki
May 2008
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12. APPENDIX

Data collection form and questionnaire\(^1\)

Oral cancer in Tehran Iran: an approach for understanding the disease burden

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\(^1\) Combined version of the data collection form and questionnaire for oral cancer patients
1. Personal characteristics:
   1.1. Sex: male--- female---
   1.2. Year of birth: "--------"
   1.3. Place of residence: Urban--- Rural---
   1.4. Marital status: Single--- married---
   1.5. Family name: "------------------- name: "-------------------"
   1.6. Father’s name: "-------------------"
   1.7. Residential full address: "---------------------------------------------------------------------"
   1.8. Phone number: "-------------------"

[Items 1.5. to 1.8. were retrieved for patients studied for their survival status.]

2. Tobacco Smoking:
   2.1. History of smoking: Never been a smoker--- Former smoker--- Smoker---
   2.2. If former smoker: have not smoked for "---" years
   2.3. If smoker, the duration: "---" years

3. Dental service utilization:
   3.1. When was your last dental visit?
       Within 6 months--- 6 months to 1 year ago--- 1-2 years ago--- 2 to 5 years ago---
       more than 5 years ago--- never--- don't remember---
   3.1. What was the reason for your last dental visit?
       I had trouble with my teeth or gums--- for regular check up--- others (specify the
       reason) "------------------- I don't remember---"

4. Tumour characteristics:
   4.1. Primary tumour site: C00--- (C01-C02)--- C03--- C04--- (C05-C06)--- (C07-C08)---
       (C09-C10)---
   4.2. Histopathology type: SCC--- ACC--- Sarcoma--- Not specified--- Others (specify)
       "-------------------"
   4.3. T (Tumour size): TX--- T1--- T2--- T3--- T4--- Not specified---
   4.4. N (Nodal involvement): NX--- N0--- N1--- N2--- N3--- Not specified---
   4.5. M (Metastasis): MX--- M0--- M1---
   4.6. Overall tumour stage: I--- II--- III--- IV--- I or II--- III or IV--- Not specified---
5. Initial symptoms:
   Pain--- swelling without pain--- ulceration--- white lesion--- Other (specify)-----------------
   none--- don't know---

6. Initial dental or medical professional visited by the patient:
   Dentist--- Physician--- Oral and maxillofacial surgeon--- Others (specify) --------
   don't remember------

7. Time between first noticing symptoms to final diagnosis:
   7.1. The date of first noticing symptoms: ---/---/ --- (dd/mm/yy) don't remember---
       not noticing any symptoms---
   7.2. The date of first professional visit: ---/---/ --- (dd/mm/yy) don't remember---
   7.3. The date of diagnosis: ---/---/ --- (dd/mm/yy) don't remember---

8. History of Treatment for the malignancy:
   8.1. Surgery: No--- Yes---
   8.2. Radiotherapy: No--- Yes--- if yes, preoperative--- postoperative---
   8.3. Chemotherapy: No--- Yes---
   8.4. Recurrent tumour history: No--- Yes--- not mentioned---
   8.5 Previous treatment for malignancies? No----Yes--- if yes what? ---------------
       don't remember---
   8.6. Final admittance date to the hospital: ---/---/ --- (dd/mm/yy) don't remember---

9. Survival status:
   9.1. Alive --- dead--- lost to follow-up ---
   9.2. Date of death: ---/ ---/ --- (dd/mm/yy)
   9.3. Cause of death: ------------------------