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Delays in oral cavity cancer

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Abstract. While the prognosis for early-stage oral cavity cancer is relatively good; the majority of patients are still diagnosed with advanced-stage disease on presentation with an associated poorer prognosis. The aims of this review are to summarize our current understanding of delays in oral cavity cancer and their impact on stage at diagnosis and survival. The delays pathway can be subdivided into three components: patient, professional, and treatment delays. Patient delay represents the longest interval in the delays pathway usually lasting between 2 and 5 months and being most influenced by cognitive and psychosocial factors. Professional and treatment delays are shorter in most studies, but highly variable depending on the respective healthcare system. Most studies indicate that advanced stage at diagnosis, primary treatment with radiotherapy, treatment at an academic center, and transitions in care are associated with an increased treatment delay. Based on our current understanding, a delay between definitive diagnosis and treatment of 4–6 weeks seems acceptable from an oncologic perspective. Further studies are needed to better define what a 'safe' waiting time is and to understand the psychological impact of delays for patients.

Key words: Oral cancer; squamous cell carcinoma; patient delay; professional delay; treatment delay.

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Among cancers with the highest incidence, a diagnosis of oral cancer renders one of the worst prognoses. Five-year survival rates of prostate, breast, colorectal, bladder, kidney, melanoma, lymphoma, cervical and uterine cancers are all higher than oral cancer in Canada[1]. In the United States (US) and Canada, the current 5-year survival rate for oral cancer is 63–64.5%[1,2]. Despite advances in diagnosis, surgery, and adjuvant therapy, the 5-year survival rate has only experienced modest improvements over the past 50 years. The Surveillance, Epidemiology, and End Results program of the National Cancer Institute has recorded data on oral cancer survival since 1975. From 1975 to 1977 the 5-year relative survival rate was determined to be 52.5% with subsequent 2–3% increases in survival in each of the next four decades[2].

Stage at diagnosis remains an important prognostic indicator for predicting patient survival. Survival rates for early-stage disease are approximately 84% while for advanced-stage disease they drop significantly to 39%[2]. The prognosis for early-stage disease is relatively good, but unfortunately 40–60% of patients have advanced-stage disease on presentation[3–5]. Moreover, in the past 40 years the proportion of patients presenting with advanced-stage disease has not decreased[6]. As a result, there has been great emphasis placed on reducing diagnostic and treatment delays in the head and neck oncology literature. If cancers are diagnosed and treated early, the risk of micrometastatic spread of the disease is reduced, and there is decreased treatment-associated morbidity. In addition, patients with advanced-stage oral cancer at diagnosis report significantly worse health-related quality of life scores when compared to patients treated for early-stage disease[7]. Even with easy access to the oral cavity, presence of a pre-malignant phase, and highly sensitive detection methods[8], diagnosis and treatment delays are common in oral cavity cancer.

The objective of this review is to describe the current state of knowledge concerning delays in oral cavity cancer. In doing so, we hope to identify deficiencies

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in the literature which can be addressed in future studies ultimately improving outcomes for oral cancer patients.

Definitions

Despite numerous publications on delays in oral cancer, methodological flaws in the existing literature have limited major advances in the field[9]. One such issue is the multiplicity of definitions used to describe delays and the failure of some studies to adequately define the delay period[9]. As a result, direct comparisons of results between studies is challenging and often misleading.

To date, there are no standardized definitions for describing delays. Total delay can be defined as the period from the patient's first awareness of symptoms to the initiation of therapy. Within this period numerous elements of the delay process have been defined: patient delay, referral delay, scheduling delay, diagnostic delay, provider delay, professional delay, doctor delay, system delay, therapy delay, and treatment delay[4,9]. To further complicate this matter, different end-points for delays of the same designation have been used. For instance, the end-point of professional delay has included histopathologic diagnosis, referral to a specialist, or the initiation of therapy[9,10]. Furthermore, in some studies the magnitude of delays is measured in days (continuous variable) while in others class intervals are used (e.g., >1 month or <1 month)[9].

A common end-point used to define treatment delay is the decision-to-treat (DTT) date, defined as the date on which sufficient pre-treatment testing is complete, the patient has agreed to treatment and the physician can reasonably assume that the patient will be treated[11]. This is convenient as this usually coincides with the date patients are added to the administratively tracked hospital wait list; however, it fails to capture the full wait that a patient experiences since the referral to a specialist was initiated or histologic diagnosis was achieved. Other important definitions referenced in the oncology literature are the time to treatment initiation (TTI) and the treatment package time (TPT). TTI is defined as time from date of diagnosis, based on histologic, cytologic, or immunohistochemical confirmation, to the date when curative therapy begins. TPT is defined as the total time from surgery to the completion of radiotherapy (RT).

Allison et al. proposed a patient-centered approach to standardize definitions for delays. Their definition describes a patient's journey from onset of symptoms to definitive treatment end; and includes patient delay, professional delay, and treatment delay (Fig. 1)[9]. In the following section we will discuss the literature referring to these three types of delays in oral cavity cancer.

Patient delays

Patient delay is the period of time between the patient first noticing a symptom and their first consultation with a healthcare professional (HCP) concerning that symptom[9]. Patient delay is the most significant contributor to total delay in the delay pathway (Fig. 1)[3,12,13]. A Canadian study of 102 oral and oropharyngeal cancer patients from 2005 to 2006 found the mean and median patient delay to be 21.7 and 4.5 weeks, respectively[10]. In the US, a study by Peacock et al. found that the mean patient delay was 3.5 months (range 0–730 days) and the mean total delay was 205.9 days or 6.8 months[12]. In another report from the US, Holmes et al. found that the average patient delay was 4.8 months[3]. In the United Kingdom (UK), Hollows et al. found the mean patient delay to be 22.5 weeks with 29% of patients waiting more than 3 months after the onset of symptoms to consult an HCP[14]. Similar findings in another UK study indicated that 39% of participants had patient delays greater than 3 months[15]. In a large German study with 646 participants, Friedrich et al. found that patient delay was within 3–4 months for 63.5% of patients with a mean delay of 6.3 months[16]. Comparable durations of patient delay have been reported in Asia[17,18] and in South America[19].

Studies investigating patient delays are retrospective in nature and thus are subject to recall bias. The degree of recall bias is greater as the date of data collection moves further from the date of symptom onset. However, most of the aforementioned studies fail to indicate the method of data collection (e.g., patient survey, chart review) and when the data was collected. Nonetheless, the duration of patient delay is fairly consistent in the literature with most studies indicating that patients wait an average of 2–5 months after symptom onset prior to consulting an HCP.

Determinants of patient delay

In a 2006 systematic review of patient delays, eight studies were identified that explored reasons for patient delay[20]. Tumor factors, sociodemographic and patient health-related behaviors were not associated with the duration of patient delay[20]. However, the authors concluded that the literature lacked high-quality research investigating the determinants of patient delay. A 2010 case–control study of young oral cancer patients (<45 years old) reported that the majority of patients had heard of oral cancer, but did not think their symptoms were consistent with cancer[21]. Forty percent of patients bought over-the-

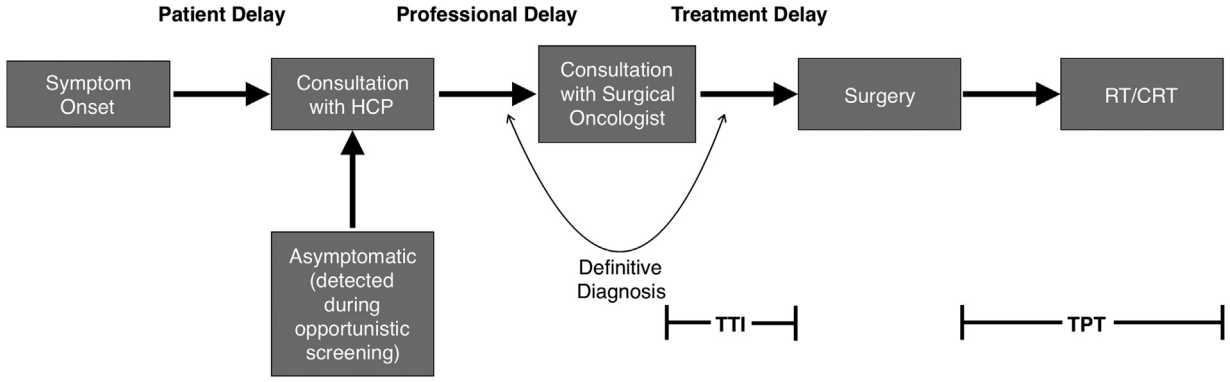

Fig. 1. Overview of key time points in the delay pathway for oral cavity cancer. CRT, chemoradiotherapy; HCP, healthcare provider; RT, radiotherapy; TTI, time to treatment initiation; TPT, treatment package time.

counter remedies before seeing a healthcare professional. Yu et al. found that female sex, and not having annual dental check-ups were associated with longer patient delays[10]. Scott et al. conducted a study where newly referred patients with potentially malignant oral symptoms were asked to complete a questionnaire addressing psychosocial factors and patient delay[15]. The results indicated that the patients' knowledge of oral cancer, severity of life events in the patient delay period, and the perceived ability to seek help for oral symptoms were all independent predictors of patient delay. Factors such as age, gender, ethnicity, smoking status, alcohol consumption, and level of education were not independent predictors of patient delay. In 2014, Panzarella et al. evaluated the role of sociodemographic (e.g., age, sex), health-related (e.g., smoking habits), cognitive (e.g., knowledge of cancer), and psychological variables (e.g., medical service mistrust) using a structured, pre-tested questionnaire in 156 oral cancer patients awaiting treatment[22]. Personal experience of cancer, unawareness, denial, and knowledge of cancer were found to be statistically significant predictors of patient delay. Similar to the results of Scott et al.[15], this study indicates that patient delay is influenced more by cognitive and psychosocial variables than by sociodemographic or health-related factors. Furthermore, recognition and interpretation of symptoms has proven to be an important factor in patient delay across all common cancers[23].

Multiple authors have explored the role of dentists and the impact of routine dental care in the oral cancer diagnostic pathway. A Canadian study found that patients who have annual dental check-ups have significantly shorter diagnostic delays[10]. Multiple other studies have suggested that having a regular dentist is associated with having an earlier-stage at diagnosis[24,25]. Gorsky et al. and Dimitroulis et al. have both reported that dentists are more likely than primary care physicians to diagnose oral cancer at an early stage[26,27]. In a 2003 investigation of patients diagnosed with oral and oropharyngeal cancer, Holmes et al. examined the differences between symptomatically driven patients and non-symptom driven patients (opportunistic screening)[3]. They found that the detection of an oral and oropharyngeal cancer during a non-symptom-driven appointment was more likely to be of an earlier-stage and was more likely to occur in a dental office. In this study, all cancers diagnosed at a physician's clinic were during symptomatically driven appointments.

The preponderance of literature suggests that oral cancer patients who have a history of regular dental appointments are more likely to have shorter diagnostic delays and be diagnosed during the asymptomatic phase of disease as a result of opportunistic screening. As a result, this patient population is more likely to have an earlier stage at diagnosis than patients who do not have regular oral examinations. Given that the majority of oral cancers are diagnosed at later stages, one can infer that many of these cancers are found as a result of symptomatically driven examinations. In the UK, Scott et al. found that 95% (233/245) of patients were identified as result of symptom-driven examinations[5]. Similar findings have also been reported in Canada[25]. In a sample of 1841 patients, 89% of patients presented due to symptoms, 5.9% were identified during opportunistic screening, and 5.1% were detected as a part of a follow-up of a previously discovered lesion[25].

Professional and treatment delays

Professional delay is the period of time between the patient's first consultation with a healthcare provider and their first consultation with the treating specialist, while treatment delay is the period of time between the patient's first consultation with the treating specialist and the initiation of ablative or palliative therapy[9]. There have been multiple descriptive studies that have probed professional and treatment delays in the context of oral cancer. A review of patients referred to the Princess Margaret Hospital in Toronto found the mean/median professional and total delays for patients with oral cancer to be 21.4/11.8 weeks and 43.1/22.5 weeks, respectively[10]. In this study, professional and total delay used the same endpoint as the date of confirmed diagnosis.

Allison et al. evaluated professional delays in upper aerodigestive tract cancers in Montreal[28]. In the patient subset with oral cancer, 71% of patients had professional delays of less than 1 month, 14.5% from 1 to 3 months, and 14.5% of patients had professional delays of greater than 3 months. They found that the presence of a comorbid illness increased the odds of a professional delay of greater than 1 month. Goldstein et al. compared the treatment delays in patients with upper aerodigestive tract cancers in Toronto in 1995 and 2005[29]. They found that the median treatment delay had increased from 25 to 37 days. A study of oral cavity cancer patients from the University of California, San Francisco found the mean delay from the time the patient visited the primary clinician to undergoing biopsy or referral was 35.9 days[12]. The average time from biopsy or referral until actually visiting the specialist was 17.7 days. The cumulative period of professional and treatment delay was 101 days. In another American study, Holmes et al. reported a much shorter period of professional delay of 2.2 weeks[3].

Data from a regional cancer registry in Italy demonstrated a median TTI of 28 days[30]. Variables associated with a longer TTI were advanced-staged cancer, treatment in an academic center, primary treatment with radiotherapy (RT) or chemoradiotherapy (CRT), and a transition of care. Patel and Brennan investigated the professional and treatment delays associated with the care of head and neck squamous cell carcinoma (HNSCC) patients at a tertiary-care public hospital in the US[31]. Median duration to key time points including date to biopsy, date to pathology finalized, date to computed tomography scans, date to diagnostic discussion with the patient, and date to treatment initiation were 8, 14, 18, 23, and 56 days, respectively, from the first physician visit. The median delay from the date of biopsy to treatment initiation was 48 days for all head and neck sites and 37 days for oral cavity. The authors reported primary treatment with RT, advanced staged cancer, and biopsy performed at the treating institution as statistically significant determinants of treatment delays.

A 2015 review of the National Cancer Database (NCDB) between 1998 and 2011 found the median TTI to be 26 days increasing from 19 to 30 days over the review period for selected head and neck sites[32]. The median TTI by site was 28, 26, 29, 23, and 29 days for the oral tongue, oropharynx (tonsil), oropharynx (non-tonsil), larynx, and hypopharynx sites, respectively. The strongest predictors of increased TTI were primary treatment with RT or CRT, a transition in care, Hispanic ethnicity, advanced-stage disease and treatment at an academic facility. The authors surmised the increased TTI over the study period is a product of three main factors: increased sophistication and number of pretreatment radiologic and pathologic investigations, increased use and complexity of multimodal therapies, and increased transitions of care.

Many centers have developed strategies aimed at reducing the professional and treatment delays experienced by patients. In the US, Ohlstein et al. implemented a patient-centric navigation system with a goal of a establishing a treatment plan with

the patient within 2 weeks of referral[33]. A clinic nurse, designated as the 'patient navigator', establishes patient contact within 1–2 days of referral, and coordinates the necessary diagnostic testing such that the patient can be presented to tumor board and an agreed-upon treatment can be established within 2 weeks of referral. Fifty-one percent of patients were found to have met this target in their review. Significant outliers were found to be patients with synchronous lung nodules and patients with extensive psychosocial needs.

Relationship between delay and disease stage

As previously described, the duration of delays is substantial and beyond what most would consider acceptable. How these delays affect the stage at diagnosis and mortality is less clear. The results of studies investigating these matters are equivocal and controversial. In 2009, Goy et al. published a systematic review that examined the relationship between delays and disease extension[34]. Of the 15 studies that met the inclusion criteria, four studies evaluated total delay and observed no statistically significant difference in the stage at diagnosis. Eight of the 10 studies that examined the relationship between patient delay and stage at diagnosis failed to observe a significant association. Of the eight studies that investigated the relationship between provider delay and stage at diagnosis, two studies found no association, three studies suggested an inverse relationship, and three studies found a positive trend between delay and stage at diagnosis.

One of the first groups to investigate the relationship between delays and stage at diagnosis was Guggenheimer et al. in 1989[35]. In their sample of 149 oral and oropharyngeal cancer patients, they found that the length of delay was not related to the tumor T stage at diagnosis. Similarly, several reports that followed failed to demonstrate a relationship between patient delay and stage at diagnosis[17,18,27,36,13,37,38]. The first study to find a positive association between delay and stage at diagnosis was by Kowalski et al. in 1994[36]. Overall, patient and professional delays were not associated with a more advanced stage at diagnosis in oral and oropharyngeal cancers. However, when only oral cavity and lip cancers were included in the analysis, professional delays of greater than 1 month had 3.02- and 4.22-times greater odds of having an advanced-stage for lip and oral cancers, respectively. Similar results were reported in Canada by Allison et al.[13]. A professional delay of greater than 3 months was associated with three-times greater odds of advanced-stage disease compared with those with less than 1 month of delay[13]. Additionally, there was a trend of increasing risk of advanced-stage disease with increasing total delays with the exception of the greater than 12-month category whose risk approximated the 1- to 3-month and 3- to 6-month categories. Like the findings of Kowalski et al.[36], there was no conclusive association between patient delay and advanced-stage disease at diagnosis. In this study, the majority of patients were classified as having early-stage disease on presentation[36]. Allison et al. suggested that a large proportion of patients were considered early-stage at initial presentation to an HCP, but the effect of the professional delay was responsible for many of these patients becoming advanced-stage by the time of histopathological diagnosis. A more recent study of 88 oral cancer patients, by Seoane-Romero et al. found that total diagnostic delay (from symptom onset to histopathological diagnosis) was not associated with an increased risk of advanced-stage disease at diagnosis[37]. The median total diagnostic delay was used as the cut-off point in classifying patients as delayed or non-delayed.

There is an absence of a consistent relationship between delays and tumor stage at diagnosis. The possible explanations for this have been discussed and appear to be multiple. One such explanation is the presence of methodological flaws in the existing literature. Many reports use different definitions of delays with different end-points and as a result are subject to misclassification. The study designs are retrospective in nature and patient delay, in particular, is susceptible to recall bias. The date of data collection is often significantly different than the date of symptoms onset[35]. The date of onset of symptoms is highly subjective and is likely influenced by many social and cultural factors[38]. A lack of association between delays and stage at diagnosis may be related to small sample sizes or the over-classification of delays into subgroups with insufficient sample sizes[9]. Moreover, heterogeneity has also contributed to a lack of a consistent relationship between delay and stage at diagnosis. Some studies have combined the oral cavity site with other upper aerodigestive tract sites. There is evidence also to suggest that within the oral cavity certain subsites are more likely to be associated with an advanced-stage at diagnosis[37].

One study indicated that the floor of the mouth, gingivae, and retromolar trigone were independent predictors of advanced stage at diagnosis[37]. The gingival location is often subject to an advanced stage at diagnosis as a result of early invasion into the adjacent bone without a necessarily long delay period[37]. Furthermore, some oral sites may be more amenable to self-exploration and self-detection, prompting patients to seek medical attention resulting in an earlier stage at diagnosis.

Some authors have proposed that the underlying tumor biology is likely an important element in the explanation for the lack of a definitive relationship between disease stage at presentation and delay duration. Two major theories have been proposed to explain this phenomenon[5]. If it is assumed that tumors become symptomatic at similar thresholds for most patients, the confounding factor may be the intrinsic aggressiveness of the cancer. For instance, an aggressive tumor may proceed to an advanced stage quickly with little diagnostic delay while a more indolent cancer may be subject to a long diagnostic delay yet still be diagnosed at an early stage as a result of the low proliferative activity of the tumor. More aggressive tumors are more likely to present with alarming symptoms such as neck mass, reducing the period of patient delay while still having an advanced-stage diagnosis. Poor differentiation, an indicator of tumor biology, have shown to be predictive of advance stage at diagnosis independent of delays[37]. Furthermore, the Ki-67 score, a measure of proliferative activity, has proven to be an independent predictor of patient survival regardless of diagnostic delays[39].

A second explanation for the discordance between delays and stage at diagnosis is the 'silent tumor hypothesis.' Some oral cancers may be asymptomatic at the onset of disease and in the early stages and only become symptomatic at an advanced stage. Some alert patients may become aware of lesions early on and despite long delays still present with early-stage disease. Meanwhile, other tumors may become symptomatic late when an advanced-stage has already been attained. Scott et al. tested this hypothesis by investigating whether certain demographic groups were more prone to advanced-stage disease[5]. They found that women had more than a 60% decrease in the risk of having advanced-stage disease regardless of the duration of diagnostic delay. The authors contend that this finding lends support to the silent-tumor hypothesis as it demonstrates that certain populations may

be susceptible to late symptom awareness (i.e. men), while other groups are more cognizant of physical symptoms (i.e. women). Moreover, there is evidence to support the theory that women have higher somatic awareness of physical symptoms in general[40].

Relationship between delay and survival

There have been very few studies to date that have evaluated the influence of delays in oral cavity cancer on patient mortality. These few studies have failed to show a relationship between delays and survival[4,6,39,41,42]. Teppo et al. investigated the relationship between patient and professional delays in 62 patients with tongue cancer and found no statistically significant difference in 2- and 5-year survival rates[41].

Van Harten et al. evaluated the impact of treatment delays on prognosis in a 2014 study of 2493 patients treated for HNSCC[4]. Patients with a TTI of 30 days or less were associated with diminished disease specific survival [hazard ratio (HR) = 0.838; 95% confidence interval (CI) = 0.697–0.92]. One explanation for this paradoxical finding is that patients with more aggressive tumors, as suggested by factors such as a history of pain or rapid tumor progression, were selected and treated more promptly.

Kowalski et al. identified 69 patients who had upper aerodigestive tract cancers that were upstaged as a result of a prolonged treatment delay[42]. These patients were matched by tumor site and initial clinical stage with patients who received treatment within 1–3 weeks. With regard to oral cavity cancers, a significant reduction in survival was demonstrated when the delay in beginning treatment resulted in clinical upstaging.

Fujiwara et al. used the NCDB to identify 4868 oral cavity SCC patients from 1998 to 2011 and analyzed key time points in the delay pathway[43]. An increase in TTI however was not found to decreased overall survival (OS) (HR = 0.98; 95% CI = 0.88–1.09). Delay in RT duration was the only variable reported to have statistically significant association with decreased OS (HR = 1.21; 95% CI = 1.03–1.44) in this study.

In the Netherlands, the Dutch Head and Neck Society proposed that 80% of head and neck cancers should be treated within 30 days of diagnosis[44]. A review of the Netherlands Cancer Registry from 2005 to 2011, which included 13,140 head and neck cancers, found that only 36% of patients met this target and the mean TTI was 37 days[44]. They found that with every 7 days of increased waiting time there was a statistically significant increase in hazard of dying (HR = 1.07; 95% CI = 1.06–1.08). The hazard of dying also rose precipitously with delays beyond 60 days. The authors reported no statistically significant difference in survival between patients treated before or after the proposed 30-day guideline. Transitions in care were associated with an increased TTI. The authors reported that patients who transitioned to a head and neck oncology center (HNOC) for treatment, after getting diagnosed at a non-HNOC, had better overall survival compared to who did not (HR = 0.89; 95% CI = 0.82–0.98). Interestingly, an increase hazard was reported for patients who transitioned from a HNOC to non-HNOC for treatment (HR = 1.33; 95% CI = 1.12–1.58), compared to patients diagnosed and treated at a non-HNOC.

A 2016 review of the NCDB examined the impact of TTI on OS of 51,655 patients undergoing curative therapy for HNSCC[45]. A TTI of 61–90 days (HR = 1.13; 95% CI = 1.08–1.19), and greater than 90 days (HR = 1.29; 95% CI = 1.21–1.38), were found to be significant predictors of death when compared to a TTI of 0–30 days. Similar to the aforementioned 2015 Dutch study[44], care transitions were associated with improved OS as was treatment in academic facilities despite prolonged TTI. The impact of TTI on OS was also found to be more detrimental in patients with early-stage disease. The authors suggested that the prolonged TTI in patients with stage I and II disease may be associated with lymph node dissemination and upstaging resulting in decreased OS.

Guidelines for professional and treatment delays

Many jurisdictions have proposed guidelines or targets pertaining to professional and treatment delays for the delivery of cancer care. These guidelines, however, are for the most part not specific to oral cavity or HNSCC. In the UK, the Cancer Reform Strategy (2007) published targets which included a maximum of a 2-week wait to see a specialist for all patients referred with suspected cancer symptoms, and a maximum of 31 days from decision-to-treat date to definitive treatment[46]. Cancer Care Ontario recognized that the biologic behavior of all cancers is unique and developed a graduated system based on the perceived urgency (Table 1)[11]. HNSCC would typically be classified as urgency category III with a target of 6 weeks from the date of consultation with a specialist to definitive treatment. The authors of this guideline conceded that there is little medical evidence on which to base their recommendations and at this time it remains largely expert opinion.

There is literature that suggests that HNSCC patients experience significant levels of psychological distress that is often decreased following the completion of treatment[47]. Moreover, prolonged waiting times negatively affect patient satisfaction and quality of life[48]. As such, it would seem reasonable to attempt to commence definitive cancer therapy with the minimal delay possible thereby minimizing psychological distress and its long-term sequelae. However, expedited referral networks, and rapid diagnostic work-up and staging may increase short-term costs incurred to publicly funded healthcare systems. Consequently, in determining an appropriate wait time it is thus a fine balance between initiating treatment in a prompt fashion to promote psychological wellbeing and oncologic 'safety,' while at the same time not placing undue stress on publicly funded healthcare systems. This optimal balance has yet to be fully elucidated.

The early literature, which consisted of single-institution studies, failed to demonstrate a relationship between delays and decreased survival. Emerging evidence from national cancer registries in the Netherlands and the US support the hypothesis that prolonged TTI, particularly beyond 2 months, adversely impact patient survival in HNSCC. Based on the current state of knowledge, a delay between definitive diagnosis and treatment initiation of 4–6 weeks seems acceptable from an oncologic perspective.

In conclusion, despite an extensive body of research, methodological flaws, particularly in the early literature, have limited advancement in our understanding of delays in oral cavity cancer. The majority of patients wait 2–5 months after symptoms onset prior to consulting an HCP.

Cognitive and psychosocial factors, such as a patient's previous experience or exposure to cancer, seem to be important determinants of the duration of delay. Having routine dental care appears to be protective as opportunistic screening facilitates the identification malignant and oral potentially malignant disorders during the asymptomatic phase of disease resulting in an earlier stage at diagnosis. Patient delays represent the longest time point in the delay pathway. As a result, researchers and policy makers alike have the potential

Table 1. Cancer Care Ontario recommended target wait times.[11]

Urgency category	Clinical conditions	Consult to decision-to-treat (days)	Ready-to-treat to operation (days)
I	Patients requiring surgery to remove known or suspected cancers that have immediately life-threatening conditions (e.g., airway obstruction, hemorrhage, neurological compromise)	Immediate	Immediate
II	Patients diagnosed with very aggressive tumors, such as central nervous system cancer	14	14
III	All patients with known or suspected invasive cancer that does not meet the criteria of urgency category II or IV	14	28
IV	Patients diagnosed with indolent tumors	14	84

to make the largest impact by targeting the delays associated with this interval.

Unlike patient delays, there is a necessary period of professional and treatment delay required for diagnosis, staging, and patient optimization prior to treatment initiation. Most existing guidelines from regional health authorities are generic, not specific to oral cancer, and are based on low levels of evidence. The actual duration of professional and treatment delay varies widely in the literature, but in general, it appears to be unacceptably long. How these delays impact stage at diagnosis, survival, and mental health in oral cancer patients is less clear at this time. Recent, studies derived from national cancer registries seem to indicate that delays beyond 4–6 weeks may result in a decreased OS. Future research should aim to better define what a 'safe' waiting time is for referral, diagnostic work-up, and treatment initiation in oral cavity cancer. In addition, more studies are needed to better understand the relationship between delays and patient-centered outcomes as well as the economic implications of accelerated-care pathways in publicly funded healthcare systems.

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None.

Ethical approval

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Patient consent

Not required.

References

1. Canadian Cancer Society's Advisory Committee on Cancer Statistics. *Canadian cancer statistics 2017*. Canadian Cancer Society; 2017.
2. Howlader NNA, Krapcho M, Miller D, Bishop K, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA, editors. SEER cancer statistics review, 1975–2014, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2014/, based on November 2016 SEER data submission, posted to the SEER web site, April 2017.
3. Holmes JD, Dierks EJ, Homer LD, Potter BE. Is detection of oral and oropharyngeal squamous cancer by a dental health care provider associated with a lower stage at diagnosis? *J Oral Maxillofac Surg* 2003;**61**:285–91. http://dx.doi.org/10.1053/joms.2003.50056.
4. van Harten MC, de Ridder M, Hamming-Vrieze O, Smeele LE, Balm AJ, van den Brekel MW. The association of treatment delay and prognosis in head and neck squamous cell carcinoma (hnscc) patients in a dutch comprehensive cancer center. *Oral Oncol* 2014;**50**:282–90. http://dx.doi.org/10.1016/j.oraloncology.2013.12.018.
5. Scott SE, Grunfeld EA, McGurk M. The idiosyncratic relationship between diagnostic delay and stage of oral squamous cell carcinoma. *Oral Oncol* 2005;**41**:396–403. http://dx.doi.org/10.1016/j.oraloncology.2004.10.010.
6. McGurk M, Chan C, Jones J, O'Regan E, Sherriff M. Delay in diagnosis and its effect on outcome in head and neck cancer. *Br J Oral Maxillofac Surg* 2005;**43**:281–4. http://dx.doi.org/10.1016/j.bjoms.2004.01.016.
7. Hammerlid E, Bjordal K, Ahlner-Elmqvist M, Boysen M, Evensen JF, Biorklund A, Jannert M, Kaasa S, Sullivan M, Westin T. A prospective study of quality of life in head and neck cancer patients. Part i: At diagnosis. *Laryngoscope* 2001;**111**:669.
8. Lingen MW, Kalmar JR, Karrison T, Speight PM. Critical evaluation of diagnostic aids for the detection of oral cancer. *Oral Oncol* 2008;**44**:10–22. http://dx.doi.org/10.1016/j.oraloncology.2007.06.011.
9. Allison P, Locker D, Feine JS. The role of diagnostic delays in the prognosis of oral cancer: A review of the literature. *Oral Oncol* 1998;**34**:161–70.
10. Yu T, Wood RE, Tenenbaum HC. Delays in diagnosis of head and neck cancers. *J Can Dent Assoc* 2008;**74**:61.
11. Cancer Care Ontario. *Target wait times for cancer surgery in Ontario*. 2006. https://archive.cancercare.on.ca [Accessibility verified October 8, 2018].
12. Peacock ZS, Pogrel MA, Schmidt BL. Exploring the reasons for delay in treatment of oral cancer. *J Am Dent Assoc* 2008;**139**:1346–52.
13. Allison P, Franco E, Black M, Feine J. The role of professional diagnostic delays in the prognosis of upper aerodigestive tract carcinoma. *Oral Oncol* 1998;**34**:147–53.
14. Hollows P, McAndrew PG, Perini MG. Delays in the referral and treatment of oral squamous cell carcinoma. *Br Dent J* 2000;**188**:262–5.
15. Scott S, McGurk M, Grunfeld E. Patient delay for potentially malignant oral symptoms. *Eur J Oral Sci* 2008;**116**:141–7. http://dx.doi.org/10.1111/j.1600-0722.2007.00520.x.
16. Friedrich RE. Delay in diagnosis and referral patterns of 646 patients with oral and maxillofacial cancer: A report from a single institution in Hamburg, Germany. *Anticancer Res* 2010;**30**:1833–6.
17. Kerdpon D, Sriplung H. Factors related to advanced stage oral squamous cell carcinoma in southern thailand. *Oral Oncol* 2001;**37**:216–21.
18. Onizawa K, Nishihara K, Yamagata K, Yusa H, Yanagawa T, Yoshida H. Factors associated with diagnostic delay of oral squamous cell carcinoma. *Oral Oncology* 2003;**39**:781–8. http://dx.doi.org/10.1016/s1368-8375(03)00075-7.
19. Morelatto RA, Herrera MC, Fernandez EN, Corball AG, Lopez de Blanc SA. Diagnostic delay of oral squamous cell carcinoma in two diagnosis centers in Cordoba Argentina. *J Oral Pathol Med* 2007;**36**:405–8. http://dx.doi.org/10.1111/j.1600-0714.2007.00547.x.
20. Scott SE, Grunfeld EA, McGurk M. Patient's delay in oral cancer: A systematic review. *Community Dent Oral Epidemiol* 2006;**34**:337–43. http://dx.doi.org/10.1111/j.1600-0528.2006.00290.x.
21. Grant E, Silver K, Bauld L, Day R, Warnakulasuriya S. The experiences of young oral cancer patients in Scotland: Symptom recognition and delays in seeking professional help. *Br Dent J* 2010;**208**:465–71. http://dx.doi.org/10.1038/sj.bdj.2010.450.

22. Panzarella V, Pizzo G, Calvino F, Compilato D, Colella G, Campisi G. Diagnostic delay in oral squamous cell carcinoma: The role of cognitive and psychological variables. *Int J Oral Sci* 2014;**6**:39–45. http://dx.doi.org/10.1038/ijos.2013.88.
23. Macleod U, Mitchell ED, Burgess C, Macdonald S, Ramirez AJ. Risk factors for delayed presentation and referral of symptomatic cancer: Evidence for common cancers. *Br J Cancer* 2009;**101**(Suppl 2):S92–101. http://dx.doi.org/10.1038/sj.bjc.6605398.
24. Langevin SM, Michaud DS, Eliot M, Peters ES, McClean MD, Kelsey KT. Regular dental visits are associated with earlier stage at diagnosis for oral and pharyngeal cancer. *Cancer Causes Control* 2012;**23**:1821–9. http://dx.doi.org/10.1007/s10552-012-0061-4.
25. Groome PA, Rohland SL, Hall SF, Irish J, Mackillop WJ, O'Sullivan B. A population-based study of factors associated with early versus late stage oral cavity cancer diagnoses. *Oral Oncol* 2011;**47**:642–7. http://dx.doi.org/10.1016/j.oraloncology.2011.04.018.
26. Gorsky M, Dayan D. Referral delay in diagnosis of oro/oropharyngeal cancer in Israel. *Eur J Cancer B Oral Oncol* 1995;**31B**:166–8.
27. Dimitroulis G, Reade P, Wiesenfeld D. Referral patterns of patients with oral squamous cell carcinoma, Australia. *Eur J Cancer B Oral Oncol* 1992;**28B**:23–7.
28. Allison P, Franco E, Feine J. Predictors of professional diagnostic delays for upper aerodigestive tract carcinoma. *Oral Oncol* 1998;**34**:127–32.
29. Goldstein D, Jeremic G, Werger J, Irish J. Wait times in the diagnosis and treatment of head and neck cancer: Comparison between wait times in 1995 and 2005—a prospective study. *J Otolaryngol* 2007;**36**:336–43. http://dx.doi.org/10.2310/7070.2007.0053.
30. Polesel J, Furlan C, Birri S, Giacomarra V, Vaccher E, Grando G, Gobitti C, Navarria F, Schioppa O, Minatel E, Bidoli E, Barzan L, Franchin G. The impact of time to treatment initiation on survival from head and neck cancer in north-eastern Italy. *Oral Oncol* 2017;**67**:175–82. http://dx.doi.org/10.1016/j.oraloncology.2017.02.009.
31. Patel UA, Brennan TE. Disparities in head and neck cancer: Assessing delay in treatment initiation. *Laryngoscope* 2012;**122**:1756–60. http://dx.doi.org/10.1002/lary.23357.
32. Murphy CT, Galloway TJ, Handorf EA, Wang L, Mehra R, Flieder DB, Ridge JA. Increasing time to treatment initiation for head and neck cancer: An analysis of the national cancer database. *Cancer* 2015;**121**:1204–13. http://dx.doi.org/10.1002/cncr.29191.
33. Ohlstein JF, Brody-Camp S, Friedman S, Levy JM, Buell JF, Friedlander P. Initial experience of a patient navigation model for head and neck cancer. *JAMA Otolaryngol Head Neck Surg* 2015;**141**:804–9. http://dx.doi.org/10.1001/jamaoto.2015.1467.
34. Goy J, Hall SF, Feldman-Stewart D, Groome PA. Diagnostic delay and disease stage in head and neck cancer: A systematic review. *Laryngoscope* 2009;**119**:889–98. http://dx.doi.org/10.1002/lary.20185.
35. Guggenheimer J, Verbin RS, Johnson JT, Horkowitz CA, Myers EN. Factors delaying the diagnosis of oral and oropharyngeal carcinomas. *Cancer* 1989;**64**:932–5.
36. Kowalski LP, Franco EL, Torloni H, Fava AS, de Andrade Sobrinho J, Ramos G, Oliveira BV, Curado MP. Lateness of diagnosis of oral and oropharyngeal carcinoma: Factors related to the tumour, the patient and health professionals. *Eur J Cancer B Oral Oncol* 1994;**30B**:167–73.
37. Seoane-Romero JM, Vazquez-Mahia I, Seoane J, Varela-Centelles P, Tomas I, Lopez-Cedrun JL. Factors related to late stage diagnosis of oral squamous cell carcinoma. *Med Oral Patol Oral Cir Bucal* 2012: e35–40. http://dx.doi.org/10.4317/medoral.17399.
38. Carvalho AL, Pintos J, Schlecht NF, Oliveira BV, Fava AS, Curado MP, Kowalski LP, Franco EL. Predictive factors for diagnosis of advanced-stage squamous cell carcinoma of the head and neck. *Arch Otolaryngol Head Neck Surg* 2002;**128**:313–8.
39. Seoane J, Pita-Fernandez S, Gomez I, Vazquez I, Lopez-Cedrun JL, De Agustin D, Varela-Centelles P. Proliferative activity and diagnostic delay in oral cancer. *Head Neck* 2010;**32**:1377–84. http://dx.doi.org/10.1002/hed.21338.
40. van Wijk CM, Kolk AM. Sex differences in physical symptoms: The contribution of symptom perception theory. *Soc Sci Med* 1997;**45**:231–46.
41. Teppo H, Alho OP. Relative importance of diagnostic delays in different head and neck cancers. *Clin Otolaryngol* 2008;**33**:325–30. http://dx.doi.org/10.1111/j.1749-4486.2008.01704.x.
42. Kowalski LP, Carvalho AL. Infuence of time delay and clinical upstaging in the prognosis of head and neck cancer. *Oral Oncol* 2001:94–8.
43. Fujiwara RJ, Judson BL, Yarbrough WG, Husain Z, Mehra S. Treatment delays in oral cavity squamous cell carcinoma and association with survival. *Head Neck* 2017;**39**:639–46. http://dx.doi.org/10.1002/hed.24608.
44. van Harten MC, Hoebers FJ, Kross KW, van Werkhoven ED, van den Brekel MW, van Dijk BA. Determinants of treatment waiting times for head and neck cancer in the netherlands and their relation to survival. *Oral Oncol* 2015;**51**:272–8. http://dx.doi.org/10.1016/j.oraloncology.2014.12.003.
45. Murphy CT, Galloway TJ, Handorf EA, Egleston BL, Wang LS, Mehra R, Flieder DB, Ridge JA. Survival impact of increasing time to treatment initiation for patients with head and neck cancer in the united states. *J Clin Oncol* 2016;**34**:169–78. http://dx.doi.org/10.1200/JCO.2015.61.5906.
46. Department of Health (UK). *Cancer reform strategy*. 2007. https://www.nhs.uk/NHSEngland/ [Accessibility verified October 8, 2018].
47. Howren MB, Christensen AJ, Karnell LH, Funk GF. Psychological factors associated with head and neck cancer treatment and survivorship: Evidence and opportunities for behavioral medicine. *J Consult Clin Psychol* 2013;**81**:299–317. http://dx.doi.org/10.1037/a0029940.
48. Robinson KM, Christensen KB, Ottesen B, Krasnik A. Diagnostic delay, quality of life and patient satisfaction among women diagnosed with endometrial or ovarian cancer: A nationwide danish study. *Qual Life Res* 2012;**21**:1519–25.

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