

Does Tumour Biological Behaviour Influence Prognosis More than Diagnostic Delay in Oral Cancer?

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Abstract: Worldwide, oral cancer has one of the lowest survival rates (lethal disease for over 50% of cases diagnosed annually) and remains unaffected despite recent therapeutic advances.

Unfortunately, almost half of the oral cancers are diagnosed at stages III or IV, probably due to delays in reaching a definitive diagnosis. Many preventive approaches (secondary prevention) have been designed assuming the logical hypothesis that the longer the diagnostic delay, the more advanced the cancer and the worse the prognosis. However, a number of studies failed to prove this association or even found an inverse relationship.

We hypothesize that tumour's biological heterogeneity in terms of aggressiveness may explain shorter delays linked to advanced stages and bad prognosis. The assumption of this hypothesis would entail favouring oral cancer and precancer screening strategies at the preclinical stage of the disease, and therefore strategies of opportunistic screening for oral cancer and precancer on asymptomatic at risk population should be reinforced.

Keywords: Mouth neoplasms, prognosis, delayed diagnosis, biological behaviour, squamous cell carcinoma.

INTRODUCTION

Oral cancer is a worldwide public health issue [1,2] whose incidence and mortality rates are steadily growing in Europe (eg: France, Hungary, Spain and Croatia), Brazil and South-Eastern Asia (Sri Lanka, Pakistan, Bangladesh and India) [3].

This neoplasm retains one of the lowest survival rate (lethal disease for over 50% of cases diagnosed annually) which remains unaffected despite recent therapeutic advances. This is particularly worrying as rising trends in oral cancer incidence are being reported for young and middle-age men from Brazil, India, certain areas of Europe and the USA [3,4].

Tumour stage at diagnosis remains the most important prognostic marker for oral squamous cell carcinoma [5]. Unfortunately, almost half of the oral cancers are diagnosed at stages III or IV with poor 5-year survival rates (20% to 50%) depending upon tumour sites, probably due to delays in reaching a diagnosis [6-9]. It has been suggested that if these malignancies were diagnosed and treated at earlier stages, survival rates would exceed 80% [10].

A number of researchers have revised the concept of diagnostic delay in head and neck cancer, however these investigations do not use homogeneous criteria

[8,9,11], and comparative analyses are not always possible [8,9]. Nowadays, the concept of delay in diagnosis is often broken into two categories, namely patient delay –the period between the patient first noticing a symptom or sign and the first consultation to a healthcare professional concerning that symptom or sign [8,9,12,13] and provider/professional delay –the period from the patient's first consultation with a healthcare provider and the definitive pathological diagnosis [12,13]. The overall diagnostic delay (total delay) would elapse from the first symptom or sign until the definitive histological diagnosis [8,9,12,13].

It seems reasonable to assume that a cancer's stage at diagnosis is a function of the length of time it had been developing prior to diagnosis (logical hypothesis). Thus the longer the delay, the more advanced the disease would be and a worse prognosis should be expected [14]. However, many studies either failed to prove this association [15-23,25] or demonstrated an inverse relationship (shorter delays linked to more advanced stages) [19,22,24,25]. Although methodological flaws could partially explain this paradox, new hypotheses seem to be necessary in this field.

THE HYPOTHESIS: BIOLOGICAL HETEROGENEITY OF ORAL CARCINOMAS

The inconsistencies observed in the association between longer delays in oral cancer diagnosis and worse outcome in terms of clinical stage and survival could be related to variability in the biological behaviour

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of these tumours. Differences in tumour aggressiveness would explain tumour's stage at diagnosis and patient survival better than the mere length of the diagnostic delay (Figure 1).

SUPPORTING THE HYPOTHESIS

Tumours of a single cancer type can appear to be similar but grow at very different rates and with different levels of aggressiveness [26]. Patients with fast-growing tumours may be diagnosed relatively rapidly, but often an advanced stage has already been reached, given the nature of the disease [24]. Shorter patient and professional delays have been associated to advanced stage at diagnosis in some oral cancer series [19,22,24,25,27,28].

We have recently demonstrated, by means of a multivariate study, that when the analysis is adjusted for tumour stage at diagnosis (I-II vs., III-IV), proliferative activity arises as an independent prognostic factor for survival and diagnostic delay does not influence this outcome [29]. These results seem to suggest that survival to oral cancer is affected more by the rapid tumour growth of the cancer than by delays in the diagnosis.

TESTING THE HYPOTHESIS

It has been suggested that cancer biology may be more important than diagnostic delay. In order to test the feasibility of this hypothesis and to assess the impact of diagnostic delay on the course of oral squamous cell carcinomas, new studies with sound epidemiologic design to minimize the biases identified in the existing reports (selection, information, confounding, survival and lead-time biases) are needed [15-25]. It is mandatory to utilize standardised criteria for measuring the diagnostic delay and to develop protocols to mitigate recall bias [8,9]. The use of structured questionnaires at the primary care level and the participation of patient relatives could increase the quality of the information on diagnostic delay [8,27,28].

It seems advisable to conduct population-based studies with an important prospective component and an adequate sample size that consider exclusively incident oral cancer cases using patient survival as the main outcome. These studies should also account for potential confounding variables, such as age, gender, tumour site, co-morbidity and treatment –including also delay during the treatment phase- because it can influence outcomes [13]. A key point to assess oral cancer heterogeneity and its biological potential is the

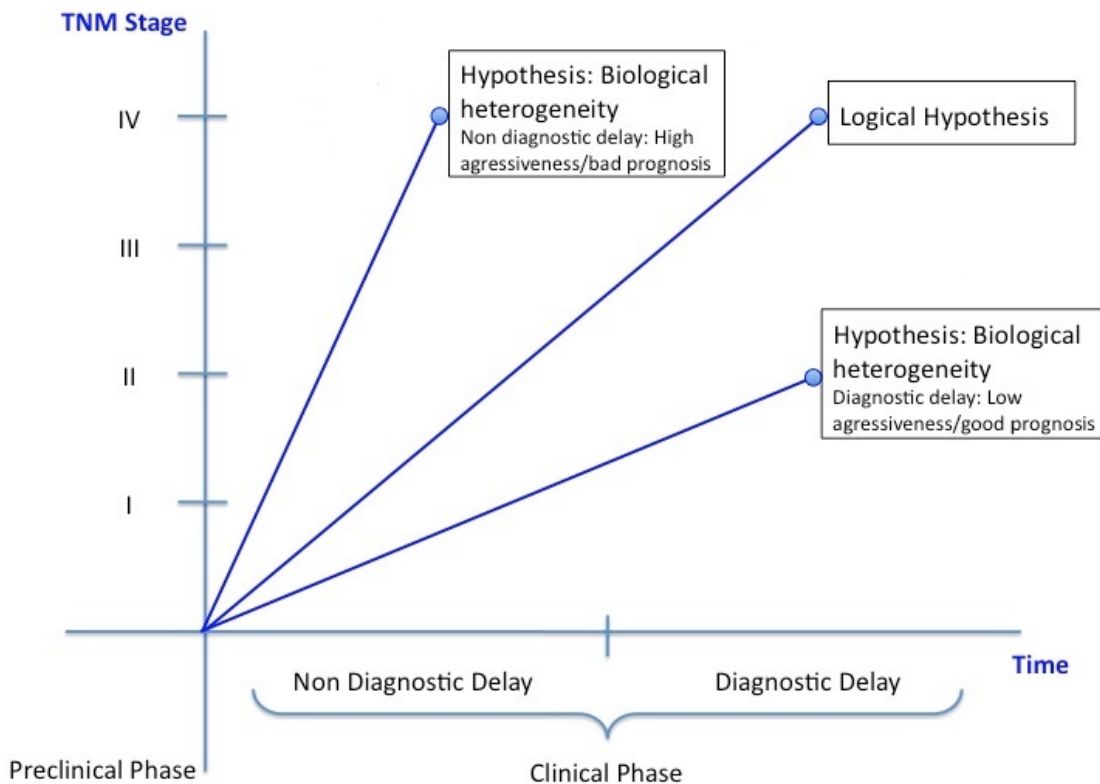


Figure 1: Hypotheses on the influence of tumour aggressiveness and diagnostic delay on disease stage at diagnosis.

histological analysis of the whole tumour, otherwise there could exist a bias, particularly in large tumours. Future studies would benefit from a quantitative analysis approach (i.e.: analysis by flow cytometry of larger tumour samples), as this procedure permits the study of the fraction of proliferating tumour cells and the amount of fraction of spontaneous cell loss, which influence the tumour's growth rate [51]. Moreover, gene expression signatures generated from DNA microarray analysis have proved to be predictive biomarkers for clinical outcome [52] and could be used to infer the clinical behaviour of the oral cancer and to adjust this way the actual weight of diagnostic delay on patient survival.

DISCUSSION

Oral cancer main features (tumour size and nodal status) appear to correlate well with tumour growth chronology [31,32]. This paradigm focused research on the possibility that diagnostic delay contributed to the spread of the disease. Despite this theory could be confirmed for a number of tumours, no definitive conclusions could be drawn for oral cancer [8,9,33-39].

Theoretical tumour growth assumes no treatment and no cell lost, but cell loss increases when a tumour grows and outstrips its blood supply. Neoplasms typically grow progressively, but even within a single tumour type there are significant variations that lead to unpredictable differences in the pattern, speed of onset, and progression of patient symptoms that would definitively condition the moment of the diagnosis [26].

When dealing with delays in diagnosis, the beginning of the study has to be the recognition of the signs and symptoms by the patient. This fact is critically affected by his/her psychosocial characteristics, some of them able to predict diagnostic delay and advanced tumour stage at diagnosis [30]. Similar findings were reported from a case-control study demonstrating that the length of diagnostic delay was significantly greater in patients with advanced tumour stages (TNM stage IV) [16].

However, there is no sound scientific evidence supporting an association between diagnostic delay in oral cancer, disease extension at diagnosis, and lower survival rates [15-25]. This fact may well be partially due to methodological flaws in the published reports to date [8,9,36,40,41].

These reports use different conceptions of diagnostic delay and are thus liable to

misclassifications, utilize retrospective designs without strategies to diminishing patient's memory bias and often break down diagnostic delay classifications into subgroups with small sample sizes. Studies involving tumours of different locations introduce confounding factors in the analysis, as the patient self-perception and self-exploration abilities depend on the site of the tumour [19,37,42]. For example, gingival locations are associated to advanced stages at diagnosis due to the early invasion of the adjacent bone tissue (T4 primary tumour), yet could present without time delay [38]. Additional difficulties come from the type of data collected (e.g.: continuous variables [19,27,30] versus categorical [41,43]), from the different sources of patient data (questionnaires, interviews, clinical records) and also from the already mentioned patient memory bias.

Different velocities of tumour growth may well also explain why some tumours remain small in size in spite of delay. Even though some studies linked diagnostic delay and advanced tumour stage, it is possible that the relationship between delay and advanced tumour stage is veiled by the fact that certain cancers remain silent during the initial stages and induce symptoms only when they reach an advanced phase (silent tumour hypothesis) [7]. This being, the tumour growth rate would act as a confounding factor in the relationship between diagnostic delay and tumour stage since patients with aggressive tumours and poor prognosis do not usually present diagnostic delay, while tumours with low proliferation rates demonstrate good prognosis despite long diagnostic delays [44,45].

Despite the aforementioned, a recent meta-analytic study by our research group has shown that diagnostic delay is broadly associated to more advanced stages in oropharyngeal cancers. This association resulted to be especially strong when the analysis was restricted to oral cancer (pooled RR, 1.47; 95%CI: 1.09 – 1.99) and when the delay was longer than one month (pooled RR, 1.69 95%CI: 1.26 – 2.77) [9]. The probability for delayed patients to present an advanced-stage oral cancer at diagnosis in this report was 25% higher than that of a non-delayed patient. Nevertheless, these data should be interpreted with caution since all 9 studies considered in the meta-analysis were cross-sectional in nature, with retrospective designs and a potential for recall bias [9].

The number of studies focusing on the relationship between diagnostic delay and survival to oral cancer are scarce, and their results show substantial

discrepancies: on the one hand the strength of the association did not reach significance [46], but on the other hand there seem to exist a strong relationship when referral delay is considered [27,47]. More specifically: when longer than a month, these delays worsen survival to oral and oropharyngeal cancer [47]. However, when tumour aggressiveness is considered, the role of diagnostic delay could not be demonstrated [29]. Moreover, confounding effects of lead-time bias could condition the association between diagnostic delay and survival to the tumour [26].

Reports on tongue cancer are particularly interesting [27,28] because the impact of diagnostic delays on survival are apparently unreasonable: shorter delays impaired survival. This paradoxical circumstance, where diagnostic delay, tumour stage and tumour prognosis are inversely related, has been previously described in endometrial, cervix, lung, colon, renal and urethral cancer, and seems to suggest that stage at diagnosis and survival are strongly affected by the biological aggressiveness of the cancer [8, 26,48].

Oral cancer is a relatively proliferating tumour with proven heterogeneity in its biological behaviour. Specifically HPV negative, aneuploid and TP53-mutated tumours have shown less favourable prognoses [49]. Moreover, the expression of different oncogenic markers including , p16, p21, p27, MDM2, MGMT, EGFR, ERBB2, RARB, MYC, BCR-ABL1, RAS, CCND1, STAT-3, and VEGF, induce a more rapid clinical course [50] that considerably reduces the opportunities for a diagnosis at early stages of the disease. Alternatively, HPV positive oral cancers, mostly oropharynx, mainly wild-type TP-53 have demonstrated favourable prognosis [49].

CONCLUSION

Advanced tumour stages in oral cancer have been conventionally ascribed to delays in reaching a diagnosis. Surprisingly, there is a lack of sound scientific evidence supporting this traditional association between diagnostic delay and disease extension and survival. However, different oral cancer genetic profiles result on a wide variability in the biological behaviour of the tumour and may justify the hypothesis of the biological heterogeneity of diagnostic delay in oral cancer.

An important issue is the difficulty in comparing oral cancer subtypes with very different behaviours. Thus rapidly growing tumours –where the quickness in

obtaining a diagnosis does not guarantee and early stage- have short periods for a potential screening, whereas slowly growing tumours permit a longer potential screening period. This circumstance should be taken into account when designing interventions aimed at reducing the duration of the diagnostic pathway.

In this sense, the corroboration of this hypothesis would imply favouring oral cancer and precancer screening strategies, and therefore opportunistic screening for oral cancer and precancer on asymptomatic, at-risk population should be reinforced.

POTENTIAL CONFLICTS OF INTEREST

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