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Mini Review

The Effect of Metastasis on Treatment and Prognosis of Oral Cancer: Short Review

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Abstract

Metastasis is the leading cause of fatality in 90% of cancers, and approximately 60% of all cancer cases will have either regional or distant metastasis at initial diagnosis. Global data shows that survival rates drop significantly with the advance of disease stage and metastatic activity; therefore, patients with localised disease have a far better prognosis than those with disseminated tumours. In this aspect, oral squamous-cell carcinoma (OSCC) is locally invasive neoplasms. Both cancers are considered the worst prognosis cancers with an overall survival rate of 50% or slightly higher. In this review, we summarise the latest data in the literature about the impact of metastasis on oral cancer prognosis and the choice of treatment, emphasising the urgent need for reliable markers for the early detection and prevention of oral neoplasms to improve the patient outcome.

Keywords: Metastasis; Oral Squamous Cell Carcinoma; Oral Cancer; Prognosis; Treatment

Introduction

Oral squamous cell carcinoma (OSCC) (ICD10 C00-C06) is considered the 6th most common cancer for both sexes [1-2]. Oral cancer is the leading cancer type and accounts for more than a third of all cancers in South-East Asian regions such as India and Sri-Lanka [3]. OSCC, which represents 90% of all oral cavity tumours, is a locally invasive lesion with its average survival rate at 50% [2]. More than 60% of oral cancer cases are diagnosed at advanced stages which decreases the survival probability significantly (Figure 1) [4-5]. The asymptomatic nature of oral cavity tumours and the delay in diagnosis/referral are the main factors contributing to the discovery of late-stage tumours that have already metastasised at the time of diagnosis [6-8].

Metastasis and oral cancer prognosis

Cervical metastasis and extracapsular spread (ECS) affect survival rate and has a great impact on both recurrence and rate of distant metastasis [9]. Several studies reported a significant reduction of survival to less than 20% in higher lymph node group or patients with ECS [9-11]. The same studies have reported an overall increase of recurrence rate of patients with either cervical metastasis or ECS, in which the group with both had the lowest survival rate as well as the worst recurrence rate of two to three times the control group [12-16].

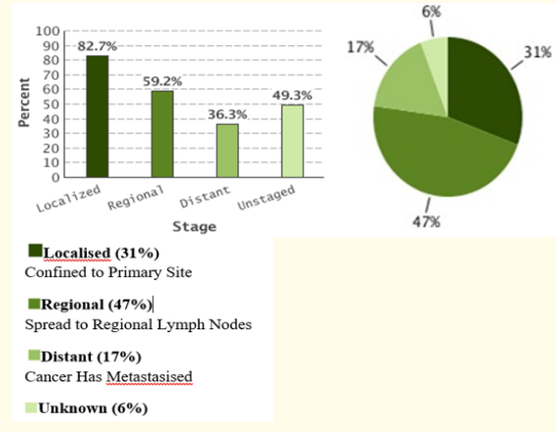

Figure 1: Percentage of survival by stage of disease and percentage of Cases by Stage at Diagnosis; Oral cavity and Pharynx Cancer SEER.

The problem of metastasis is even more complicated due to the occurrence of micro metastasis which can be in the range of 11 - 44% in T1-T2 clinically negative lymph node patients and has a deterministic effect on the prognostic outcome of the disease [17-21]. Micro metastases significantly decrease the survival rates and recurrence rates even when the most aggressive treatment modalities are in place [22-24]. Jang., et al. found that 57% of early-

stage oral cancer patients who presented with occult metastasis had decreased survival rates (24% compared with 66% for those with no micro-metastasis) despite receiving radiation treatment and neck dissection [25]. Thiele., *et al.* studied 122 patients with early-stage oral cancer, all of whom underwent neck dissection and found 17 (13.9%) patients with occult metastasis [26]. Even with neck dissection, the disease-specific survival for those patients was down to 17.8% from 61.9% for the occult-free patients.

The final form of metastasis in OSCC is distant metastasis (DM) which has been reported in a range of 3-30% prevalence among different studies [27-28]. The rate of distant metastasis at initial diagnosis of the oral tumours is estimated to be less than 3% [29-31]. The rates of distant metastasis along the course of the disease range from 9 - 30% [32-33], which might explain the huge fluctuation in the rate of metastasis reported by different studies. Another explanation might be that distant metastasis develops as a consequence of a regional metastasis in patients who fail to achieve loco-regional disease control after treatment [34-36]. It has been concluded that patients with positive lymph nodes are three to seven times more likely to develop distant metastasis [37-39]. Li., *et al.* [40] reported 1, 3 and 5-year survival rates of 56.8%, 9.1% and 6.8%, respectively for patients with DMs. Only three out of 36 patients with distant metastasis survived to the second year. The most common sites for metastasis from OSCC tumours are: lung (> 60%) followed by bone, liver, and skin [41].

Metastasis and treatment in oral cancer

The metastatic potential of OSCC is critical in the decision-making when choosing treatment, necessitating aggressive therapeutic modalities to ensure residual disease-free outcomes [42]. The risk of micro-metastasis is around 30% in early-stage cases, which significantly increases the risk of recurrence and reduces the chances of survival [17-21]. Neck dissection is suggested for elective treatment and staging of the clinically negative lymph node patients with stages I and II. However, the indications and advantages of this procedure in the head and neck area are under debate [43]. Several retrospective studies and few RCTs have been conducted to identify the benefits of this invasive procedure [44-46] (Table 1). A recent meta-analysis reported in favour of neck dissection, although several issues have been raised regarding the study design, statistical analysis and selection criteria, highlighting the need for proper randomised trials [47].

Author	Study Sample	Study Type	Recurrence Treated Vs OBS %	DSS survival	Overall survival
Smith [92], 2004	171	Retro	20 7	96 92	same
Kelner [97],2014	172	Retro	7* 15	96* 85	87^ 84
Feng[96],	229	Retro	9.6* 19.2	79.2* 61.9	20* 41
Keski-Sa¨ntti [93],2006	80	Retro	44* 20	63^ 66	82^ 77
Liu [94], 2011	13	Retro	14.8 23.2	NS	NS
Poeschl [106],2012	86	Retro	16.6 18.4	NS	NA
D'Cruz [110],2009	359	Retro	5.7* 47	74^ 68	60^ 60
Yuen [112],2009	71	RCT	6 37	89^ 87	N/A
Fakih [111],1989	70	RCT	30 58	63 52	N/A
Klingerman[95],1994	67	RCT	12 39	N/A	72* 49

* Significant results, NS. Author claimed non-significant, ^ Non-significant, N/A Data not available, DSS = disease-specific survival, Retro = retrospective, RCT = randomised control trial, OBS = observation.

Table 1: Comparison of studies performed on the outcome of neck treatment through neck dissection or observation according to survival.

Patients with advanced stages of head and neck tumours were treated with surgery and radiotherapy or radiotherapy alone for inoperable tumours, which resulted in poor survival and severe morbidity [48-49]. Pignon., *et al.* [50] performed a meta-analysis of 70 trials, including 10,741 patients, highlighting only 4% improvement in the survival of advanced-stage patients of head and neck cancers in favour of the multimodality treatment. In 2009, an updated version of the meta-analysis was been published with 24 new trials with similar results and no difference between outcomes in the previous two decades [51]. Another meta-analysis claimed that induction chemotherapy (i.e. before treatment) resulted in 7% enhancement in the distant metastasis-free rate compared with loco-regional treatment alone: however, no effect on survival was achieved [52].

Furness., *et al.* analyzed 89 randomized studies on oral and oropharyngeal cancer and found that induction or concomitant chemotherapy plus surgery and radiotherapy produced a 10 - 20% survival advantage in patients with advanced-stage neoplasms. However, the study did not show any significant improvement in terms of recurrent or metastatic control for these treatments [53]. A recent study showed an improved outcome for patients with advanced oral cancer treated with multimodality in terms of recurrence, metastasis-free and overall survival compared with those treated with mono or dual therapies [54]. The study revealed that 115 patients of 222 (51%) died due to OSCC-related causes with 58% survival advantage for surgery chemo-radiotherapy (S-CRT) group. Patients in this group achieved a 22% reduction in the recurrence rate, from 39%. The metastasis-free rate for S-CRT group was 84% but this was a secondary objective of the study and the comparison criteria were not clear. The results confirm the notion that despite a slight improvement in survival, these treatment regimens still fail to prove any advantage in recurrent oral cancer. OSCC has a higher rate of recurrence even in patients who undergo treatment [55]. Patients with recurrent diseases have a very poor prognosis, and even with the salvage treatment, the outcome remains unfavourable [56-57]. The relative success in early detection and prevention of early-stage tumours has resulted in prolonged survival periods but with more recurrence and distant metastasis incidence rates observed [58].

Conclusion

The choice of treatment is currently determined using diagnostic tools available to identify the level of the cervical metastasis. Clinical examination alone is not capable of detecting occult metastasis; therefore, adjunctive methods such as imaging should be used to diagnose such lesions. The low specificity and sensitivity of these diagnostics compels clinicians to deal with the consequences of metastasis after it has occurred. Therefore, the management of OSCC patients with metastasis, or those in early stages with high risk of metastasis, requires invasive management approaches to ensure the best outcome. Unfortunately, due to the knowledge gap in understanding metastasis, we experience more relapses with cancer treatment. Metastasis has shifted to become the prime killer of the OSCC patient, not the primary tumour itself. Molecular diagnostics (e.g. PCR, DNA microarray) are revealing higher than ever metastatic rates, up to 30%, even in very early stages, with some new opinions that metastasis commences as early as the tumour itself. Only by understanding the molecular mechanism of the pathogenesis of metastasis, can we establish any basis for precise clinical models, which will allow the identification of the critical characteristic of those cells and this is a vital requirement for development of effective therapeutic modalities.

Conflict of Interest

None Declared This article is an intellectual property of the author and this consent is to confirm the approval of the author to publish the article in the intended journal. This is also to confirm that this article has not been published before or under any publication consideration.

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