

Oral Cancer in Young vs Old Individuals: A Systematic Review

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ABSTRACT

Aim: To compare various parameters associated with oral cancer in young and old patients and systematically compile the data on prognosis or outcome of oral cancer in young and old patients that include case series, matched-pair analyses, institutional series, and database reviews.

Background: Though oral cancer is considered a disease of old age, a recent clinical scenario witnesses its increasing incidence among young persons. When compared to old patients, young patients with oral cancer are exposed to the carcinogens for a very petite period of time suggesting underlying pathogenesis to be distinct from that in older individuals. Literature reports several studies about the occurrence of oral cancer in young patients; however, no unanimous opinion exists about its prognosis and treatment outcomes when compared to older patients. Keeping this in mind, we have extensively studied all the possible aspects (location, local and regional recurrence, nodal and distant metastasis, overall survival, etc.) from the English literature and systematically compiled the available data on prognosis or outcomes of oral cancer.

Review results: The overall outcome of the case series shows poorer prognosis in young patients, matched-pair analyses, and institutional series suggesting no significant differences whereas the databases favored a better prognosis in young patients. The mean overall survival rate was found to be better for young patients in the database and institutional review whereas worse in the matched-pair analyses. The mean 5-year survival rate was found to be more in young individuals in matched-pair analyses, database reviews, and institutional series as compared to older oral cancer patients.

Conclusion: Though data extracted from various study designs are heterogeneous, the present review gives a scoping view of the papers published on oral cancer in young vs old patients. More prospective studies are suggested with a larger sample size in the future.

Clinical significance: The present review will help to better understand the nature, course, and biologic behavior of oral cancer in young patients leading to the development of specific treatment strategies to manage the patients based on their age-groups.

Keywords: Old patients, Oral cancer, Oral squamous cell carcinoma, Outcome, Prognosis, Young patients.

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INTRODUCTION

Ranked as the eighth most common cancer across the globe, oral squamous cell carcinoma (OSCC) is one of the most common malignancies worldwide.¹ In defiance of remarkable advancements in cancer genomics and treatment, this particular cancer has not been benefited much and thus continues to spread its terror with a poor overall prognosis.² Typically seen among individuals of 60 to 70 years of age, particularly males, OSCC has been reported to be strongly associated with a habit history of tobacco or alcohol consumption.³ Occurrence of OSCC in young patients is not very common; however, recent reports have divulged the prevalence of OSCC in young individuals that accounts for 3.1 to 18.8% of all cases.⁴ The pathogenesis of cancer development and progression in young individuals differs from that of older patients as they are exposed to the carcinogens such as tobacco and alcohol for a petite period of time. It is hypothesized that several other unascertained factors such as inborn genetic error of susceptibility or immunodeficiency may have a role to play.¹ Identification of such unique mechanism of carcinogenesis at the molecular level in young patients is still a topic of ongoing research.

To date, several studies have reported the occurrence of OSCC in young patients, howbeit the available data are very wide and heterogeneous to understand. No unanimous opinion exists about the prognosis and treatment outcomes of OSCC in young individuals when compared to older patients.⁵⁻⁷ This discrepancy could be partly attributed to the arbitrary use of cutoff of the patient's age in the study report, making it difficult to compare the results with other authors.¹ In the present article, we attempt to amass various studies on the occurrence of OSCC in young

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patients available in the literature. Based on the study design, we have segregated all the studies, documented and compared their outcome of prognosis in young patients with OSCC while

taking OSCC in old patients as the study control. To the best of our knowledge, this work is a first of its kind that evaluates multiple clinical and prognostic factors of OSCC in young individuals and compares the dissimilitude results among each other.

METHODS

Search Strategy and Selection Criteria

The title and details of this selected topic have been registered in PROSPERO (Reg. no. CRD42018100299). This systematic review was conducted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. We performed a wide-ranging search of the databases (PubMed, Medline, SCOPUS, Web of Science, Cochrane, and Google Scholar) along with cross-references to the published articles on the occurrence of OSCC in young patients for appropriate studies/ case reports published since 1967 till date. Keywords used for the same purpose included a combination of "OSCC in young patients," "oral squamous cell carcinoma in adults," "oral cancer prognosis," and/or "head and neck squamous cell carcinoma (HNSCC) in young individuals." Moreover, supplementary citations that were acknowledged through the lists of selected references and bibliographic linkages were also integrated with the review. We also searched for the above-mentioned keywords in journals allied to subjects such as oral pathology, oral medicine, and oral surgery. The included articles comprised of various case series matched paired analyses, database reviews, and institutional series. Case reports with a limited number of cases, narrative reviews, and articles related to the overall prognosis of OSCC in the general population were excluded from the present review. There were 238 records after screening the titles. After removing the duplicates, 52 remained that were assessed for eligibility. Out of which, six were excluded as three had only abstracts available and for the other three, relevant data were not extractable. Thus, the total number of papers included in the present systematic review is 46 (Fig. 1).

RESULTS

The results of the present systematic review have been described in four parts based on the study designs of the included papers.

Case Series (Annexure: Sheet 1)

Study Design

A total of 14 case series are included in this group that analyzed the outcome of OSCC in young patients. The studies included were published during the period range of 1967 to 2001, with a maximum number of studies conducted during 1980s⁸⁻¹⁴. The age criteria for inclusion of the young cases were not similar for all the cases, and the age limit varied from <30,^{10,15,16} <35,^{8,17} <40^{9,11-14,18-20} to <45²¹ years. In total, 329 young patients with OSCC were incorporated in this study design, with the highest number of patients included in a study by Iype et al.¹⁷ Maximum number of studies (6) included OSCC of the tongue.^{8-10,15-19} The total number of included cases does not justify HNSCC of the oropharynx and other regions. Patients who refused the treatment were not considered further in the analysis.¹⁰ Only two studies considered study controls that were older than their study patients.^{16,21}

Outcome

Seven studies (50%) showed a worse prognosis whereas six studies (42.28%) inferred no significant difference in the overall prognosis of OSCC in young and old patients. A single study⁹ concluded that it was better than in old patients.

Overall Survival

The overall survival rate of young patients with OSCC was 46.15 and 45% in the studies by Venables et al.¹⁵ and Byers,¹⁶ respectively. Of the two groups from the study by Amsterdam et al.,⁸ group A showed 43% whereas group B showed 75%, with a combined overall survival rate being no more than 55%. This suggests that the overall survival of young patients with OSCC of the tongue is much less than that of any other oral site. According to McGregor et al.,⁹

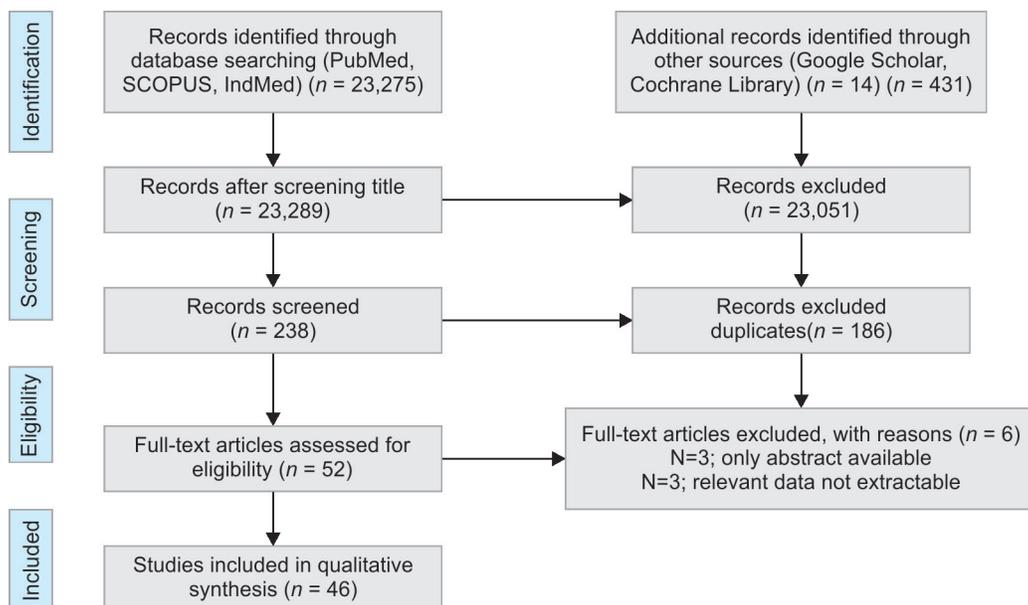


Fig. 1: PRISMA flowchart



it was 75% and that for other sites was 55.55% whereas Newman et al.¹⁰ found it to be 46%. Accordingly, Son et al.,¹¹ Benninger et al.,¹³ and Sarkaria et al.¹⁸ in their studies demonstrated 16.66, 22.20, and 33.30%, respectively. Martin-Granizo et al.²⁰ observed 75 and 85.70% with stages 1 and 2, and 50% with stages 3 and 4. Based on these observations, we concluded that the mean overall survival rate of young patients with OSCC is 45.59%.

Overall Recurrence

The overall recurrence rate in young OSCC patients was 16.66% according to Son et al.¹¹ A combined recurrence of 20% was observed in the study by Martin-Granizo et al.,²⁰ with stage 1 and 2 and stage 3 and 4 patients having an overall recurrence of 85.70 and 50%, respectively. Thus, the mean overall recurrence of OSCC in young patients is 18.33%.

Local Recurrence

Venables et al.¹⁵ observed a local recurrence in about 7.69% of the treated young patients. Twenty-nine percent of cases of group A from the study by Amsterdam et al.⁸ demonstrated local recurrence whereas none from group B showed any recurrence, together accounting for a combined rate of 18%. Newman et al.¹⁰ observed that 1 of 12 cases (8.33%) showed local recurrence whereas 69.23% in the study by McGregor et al.¹² recurred locally. With 88.80% of the recurrence rate, Benninger et al.¹³ reported the maximum local recurrence among the included case series. In the study by Cusumano et al.,¹⁴ 15.38% of the cases showed local recurrence whereas Sarkaria et al.¹⁸ and Hart et al.²¹ and Iype et al.¹⁷ found 16.60, 11.10, and 40.60%, respectively. According to our analysis, the mean local recurrence rate in young individuals with OSCC is 30.64%.

Regional Recurrence

Forty-six percent of the patients included by Venables et al.¹⁵ showed a regional recurrence at different sites whereas 55% of the patients from the study by Byers¹⁶ demonstrated regional failure. In a study by Amsterdam et al.,⁸ group A showed 71%, and group B showed 25%, with a combined rate of 55% for the total cases. McGregor et al.⁹ and Newman et al.¹⁰ found a comparable regional recurrence rate of 25%. Cusumano et al.,¹⁴ Sarkaria et al.,¹⁸ and Iype et al.¹⁷ found 15.38, 33.30, and 15.60% of cases with regional recurrence, respectively. Thus, as per our analysis, the mean regional recurrence of OSCC in young patients is 33.80%.

Locoregional Recurrence

Venables et al.¹⁵ found 30.77% cases recurring locally as well as regionally whereas Byers¹⁶ observed 18%. In the study by Newman et al.,¹⁰ 8.33% of cases showed a locoregional recurrence at different sites. A locoregional recurrence of 15.38 and 33.30% was observed in the study by Cusumano et al.¹⁴ and Sarkaria et al.,¹⁸ respectively. About 11.11% of the patients demonstrated recurrence at local and regional sites by Hart et al.²¹ Hence, our analysis concludes that the mean locoregional recurrence rate of OSCC in young individuals is 19.48%.

Two-year Survival Rate

The 2-year survival rate in the study by Venables et al.¹⁵ was 61.53% whereas it was 45% in the study by Byers.¹⁶ Of the two groups from the study by Amsterdam et al.,⁸ group A showed 57% whereas group B showed 75%; the combined 2-year survival rate of both the groups was not more than 75%. Furthermore, McGregor et al.,¹² Sarkaria et al.,¹⁸ and Hart et al.²¹ observed 31, 33.30, and 66.66%,

of 2-year survival rate, respectively. According to our analysis, the mean 2-year survival rate of young patients with OSCC is 52.08%.

Three-year Survival

Of the total young patients included by Venables et al.,¹⁵ 46.15% survived for 3 years. Only 15% survival was observed by McGregor et al.,¹² which is about half of its 2-year survival rate. In the study by Sarkaria et al.,¹⁸ it was 33.30% whereas it was 91% for Iype et al.¹⁷ Hart et al.²¹ reported survival of 55.55%. As per our analysis, the mean 3-year survival rate of young patients with OSCC is 48.28%.

Five-year Survival

Venables et al.¹⁵ and Benninger et al.¹³ reported a 5-year survival of 30.76 and 21%, respectively. Of the total patients included in the study by Amsterdam et al.,⁸ 14.28 and 75% of patients from group A and group B, respectively, survived for at least 5 years, leading to a combined 5-year survival rate of 36%. Cusumano et al.¹⁴ demonstrated 100% survival for patients with stages 1 and 2 and 16.60% with stages 3 and 4, and 70.60 and 55.55% were observed by Atula et al.¹⁹ and Hart et al.,²¹ respectively. In the study performed by Iype et al.,¹⁷ 87% of the included young OSCC patients survived for 5 years. Thus, it can be inferred from our analysis that the mean 5-year survival of young individuals with OSCC is about 52.18%.

Distant Metastasis

Metastatic tumor at a distinct site was observed in 7.69 and 18.18% of the total young OSCC patients in the study by Venables et al.¹⁵ and Byers,¹⁶ respectively. From the study by Amsterdam et al.,⁸ 71% of patients from group A and 25% of patients from group B showed metastasis at some site within the body. The combined rate of metastasis of both the groups was 55%. Thus, it can be hypothesized that OSCC of the tongue holds high chances of getting metastasized elsewhere in the body as compared to other oral sites. In the present review, the mean rate of metastasis of OSCC at some distant site is 21.79%.

Second Primary Lesions

Of the total case series included by Amsterdam et al.,⁸ five (35.71%) case studies reported the occurrence of second primary lesions later during the follow-up period. Twenty-five percent of group B patients whereas none of the cases from group A showed any second lesion, which sums up to 9%. McGregor et al.⁹ reported 3.70% with OSCC of the tongue developing a second primary lesion. Also, 4.16 and 15.38% of cases by Son et al.¹¹ and McGregor et al.,¹² respectively, showed the occurrence of a second primary lesion. According to our analysis, the mean rate of occurrence of a second primary lesion in young patients with OSCC is 9.45%.

Cancer-related Deaths

In the study by Venables et al.¹⁵ and Byers,¹⁶ 53.85 and 55% of the total young OSCC patients died, respectively. According to the reports by Amsterdam et al.,⁸ 50% of patients from group A and 25% of patients from group B died due to OSCC, with a combined rate of 41.66%. A total of 19.33% of patients died in the study by McGregor et al.,⁹ out of which 6.66% were T1 tongue, 20% were T2 tongue, and 100% were T3 tongue cancer patients, and 33.33% were with the involvement of other oral sites. Newman et al.¹⁰ observed a death rate of 58.33% whereas Son et al.¹¹ reported the highest number of deaths with 83.33% among all case series in this review. McGregor et al.¹² noted 69.23% whereas Benninger

et al.¹³ found the rate to be 77.77%. In the study by Sarkaria et al.,¹⁸ Atula et al.,¹⁹ and Iype et al.¹⁷ 66.60, 35.30, and 10.40% of patients died due to OSCC, respectively. Hence, it can be concluded that the mean rate of cancer-related deaths in young patients suffering from OSCC is 55.10%.

Matched-pair Analyses (Annexure: Sheet 2)

Study Design

A total of 16 matched-pair analyses were included in this review. The analyses were published from 1988 to 2017 with a maximum number of studies conducted after the year 2000.²²⁻³¹ The inclusion age criterion for young OSCC patients was not similar for all the analyses (<35, <40, <41, and <45 years). A study (6.25%) used <35 years³²; 10 studies (62.5%) used <40 years^{23-25,30,31,33-37}; 1 study (6.25%) included <41 years²⁸ whereas 4 studies (25%) used <45 years^{22,26,27,29} as the age criterion.

Our analysis included 1,689 young OSCC cases (299 head and neck, 225 oral cavity, 989 oral cavity and pharynx, and 176 tongue cases) and 1,110 controls (330 head and neck, 453 oral cavity, and 327 tongue cases).

Outcome

Out of the 16 analyses, 7 (43.75%) concluded that the outcome was similar for both the age-groups; 3 (18.75%) showed a better outcome in young patients whereas 6 (37.50%) analyses concluded the outcome to be worse in young patients.

Overall Survival

Kuriakose et al.³² reported the overall survival to be 89.20% in the younger and 91.90% in the older group whereas Vargas et al.³⁷ showed it to be 65 and 76%, respectively. According to our analysis, the mean overall survival rate is 77.10% in the young and 83.95% in the older OSCC group.

Matched Survival Analysis

Garavello et al.²⁵ reported the survival rate to be 34% in the young whereas 58% in older OSCC cases. Lee et al.²⁶ reported the survival in young OSCC cases was 55 ± 3 months whereas in older OSCC cases it was 36 ± 5 months.

Overall Recurrence

Vargas et al.³⁷ reported the overall recurrence rate to be higher in the young (65%) than in old OSCC cases (41%). They also noted that younger women with OSCC of the anterior tongue show a higher rate of recurrence, and the interval to recurrence is lesser than in older patients. Pytynia et al.²³ demonstrated the overall recurrence to be 19.4% in the young whereas 16.1% in older OSCC cases. In the study by Garavello et al.,²⁵ it was higher in the young (74%) than in older OSCC cases (51%). Popovtzer et al.²² reported it to be 58% in the young and 57.10% in older cases. According to our analysis, the mean overall recurrence rates in the young and old OSCC cases are 54.1 and 41.30%, respectively.

Local Recurrence

Schantz et al.³⁴ reported a local recurrence of 14.45% in the young whereas 9.63% in the older population. Garavello et al.²⁵ reported 39% in young patients whereas 24% in older group. Jeon et al.³¹ reported no local recurrence in the young; whereas, in the older group, it was 2.10%. Thus, in the present review, the mean local recurrence rate in the young and old OSCC cases is 20.63 and 21.95%, respectively.

Regional Recurrence

In the study by Schantz et al.,³⁴ 13.25% of the young and 9.63% of the old patients with OSCC showed regional recurrence. Garavello et al.²⁵ reported 26% in young patients whereas 25% in the older population. Jeon et al.³¹ found the least regional recurrence in young patients (4.3%); whereas, in the older group, it was 9.6%. Thus, in the present analysis, the mean regional recurrence rate in the young and old OSCC cases is 22.05 and 18.92%, respectively.

Locoregional Recurrence

Friedlander et al.³⁵ reported it to be 44% in the young and 22% in the old group. Jeon et al.³¹ demonstrated it to be 26% in the young and 11% in the older group. According to the analysis of overall cases, the mean locoregional recurrence rate is 35% in the younger individuals whereas 16.5% in older individuals.

Five-year Survival Rate

A 5-year survival rate of 62% among the young and 69% among old patients were found by Friedlander et al.³⁵ Jeon et al.³¹ reported it to be 42% in the young and 70% in the older group. Keegan et al.³⁰ concluded that it is more in the younger group (80.70%) than in the older group (62%). According to our analysis, the mean 5-year survival rate is 66.15% in the young whereas 63.35% in the older OSCC group.

Distant Metastasis

Verschuur et al.³⁶ reported the distant metastasis to be more in the younger group (8.10%) than in the older group (6.50%). Lee et al.²⁶ found no distant metastasis in the younger group and 10% in the older population. Jeon et al.³¹ reported it to be significantly higher in the younger group (26%) than the older group (2.10%). According to the present analysis, it is 10.37% in the younger population; whereas, in the older OSCC population, it is 11.50%.

Second Primary Lesions

3.8% of the included young OSCC cases and 6.8% of the old OSCC cases showed a second primary lesion later during the follow-up in the study conducted by Schantz et al.³⁴ whereas Verschuur et al.³⁶ reported it as 8.10 and 18.40%, respectively. According to the present analysis, 25.83% of the young and 32.06% of the old OSCC patients reported a second primary lesion.

Cancer-related Deaths

Pytynia et al.²³ reported that 25.80% of the young OSCC cases died due to cancer whereas Kuriakose et al.³² found the cancer-related death rate to be 10.80% in the young and 2.70% in adults. Ho et al.²⁷ showed the rate to be 64.30 and 5.40%, respectively, for the young and old individuals. According to the present analysis, the mean cancer-related death rate is 33.5% in the young and 27.75% in the older OSCC group.

Database Reviews (Annexure: Sheet 3)

Study Design

We included five database reviews that reported the trends of young OSCC patients. The age limit applied in a study (20%) was <20 years.³⁸ Another study (20%) used <35 years³⁹ of age whereas three studies (60%) incorporated <40 years⁴⁰⁻⁴² of age for young OSCC cases. Annertz et al.⁴¹ considered tongue cancer cases in the young group whereas studies by Schantz et al.⁴² and Lacy et al.⁴⁰ integrated cases of HNSCC including OSCC. A total of 2,026 young OSCC patients were included in this review.

Funk et al.³⁹ included 50,938 control patients in his study, of which 26,181 were middle-aged (age, 36 to 65 years) whereas 24,757 were old-aged (age, >65 years). The control group of Schantz et al.⁴² in group A was of 2,886 middle-aged patients (age, 40 to 64 years) and 3,485 old patients (age, >64 years) whereas group B included 2,212 middle-aged patients (age, 40 to 64 years) and 3,348 old-aged patients (age, >65 years).

Outcome

All the five database reviews (100%) concluded that the overall prognosis of OSCC in young patients was better than that in the older age-group.

Overall Survival

Schantz et al.⁴² in their database review reported an overall survival of 58.90 and 70.60% among the young OSCC patients of group A and group B, respectively. The same was found to be 43.20 and 49.80% for middle-aged patients and 38.20 and 45.80% for old-aged patients of group A and group B, respectively. According to our analysis, the mean overall survival for the young is 64.75%, for middle-aged patients is 46.50%, and for old-aged patients, it is 42%.

Two-year Survival

The 2-year survival of 72.30, 67.40, and 62.50% was observed by Funk et al.³⁹ for the young, middle-, and old-aged groups, respectively.

Three-year Survival

Funk et al.³⁹ further reported a 3-year survival of 67.50, 59.70, and 56%, respectively, for the young, middle-, and old-aged groups, which was subsequently less than that of their 2-year survival.

Five-year Survival

The 5-year survival of 63.70, 51, and 47.60% was noted among the young, middle-, and old-aged groups, respectively, by Funk et al.³⁹ Likewise, Annertz et al.⁴¹ reported the same to be 66, 48, and 43%. Lacy et al.⁴⁰ observed 65% among the young whereas 52 and 38% for middle-aged and old-aged groups, respectively. Morris et al.³⁸ reported 75.30% for the young in contrast to 47.10% for old patients. As per our analysis, the mean 5-year survival rate for young OSCC patients is 67.50%, and for middle-aged and old-aged patients, it is 50.33 and 43.93%, respectively.

Institutional Series (Annexure: Sheet 4)

Study Design

A total of 11 institutional series that compared the prognosis of the young and old OSCC patients were reviewed and included. The age limit varied for different institutional series. Of the total, one (9.09%) institutional series used the criterion of <30 years⁴³ of age. And 8 of 11 (72.72%) studies incorporated the <40 years^{6,44-50} of age criterion whereas 2 of 11 (18.18%) institutional series included patients who were <45 years^{51,52} of age. Seven study series considered young patients with OSCC of the tongue.^{43,44,46-48,50,51}

A total of 908 young OSCC patients and 5,656 control patients from different institutional series are included in this review.

Outcome

When the study outcome for the overall prognosis of study patients was compared among the institutional series included, we found that 7 of 11 (63.64%) included in the series found no difference in the prognosis of OSCC among the young and old patients whereas 4 (36.36%) concluded the prognosis to be better for young patients (Fig. 1).

Overall Survival

Fang et al.⁵⁰ reported the overall survival to be 66.60% for the young and 72.60% for old patients. On the contrary, Liao et al.⁴⁸ found the overall survival to be 75% in the younger group and 68% in the older group. According to the present review, the mean overall survival of the young and old OSCC patients is 70.80 and 70.30%, respectively (Graph 1).

Local Recurrence

Hyam et al.⁴⁶ showed a local failure of 13% in the young group, 21% in the middle-aged group, and 27% in the old-aged group. A local recurrence of 60% in the young and 11.18% in old patients was reported by Fang et al.⁵⁰ Veness et al.⁴⁷ and Soudry et al.⁴³ demonstrated 9.10 and 20% for the young whereas 7.70 and 30% in old patients, respectively. According to our analysis, it was 25.53% in the young and 18.97% in old OSCC patients.

Regional Recurrence

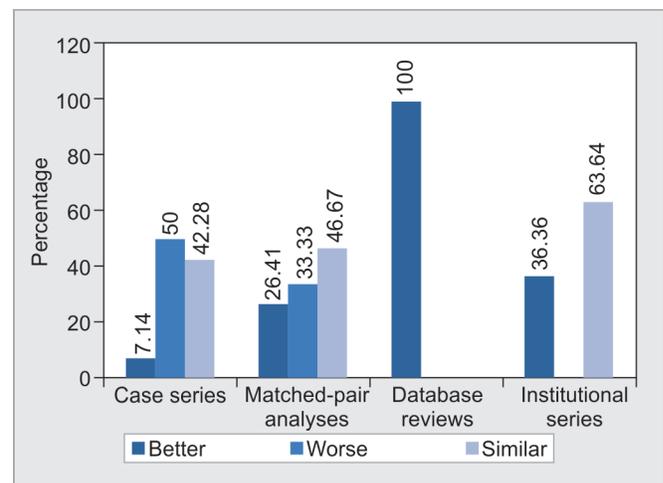
Hyam et al.⁴⁶ reported a regional recurrence of 27% in the young, 6% in middle-aged patients, and 12% in old-aged patients. In the study by Fang et al.⁵⁰ a regional failure of 6.60% in the young and 24.80% in the old group was noted. A regional recurrence of 22.70 and 19.70% by Veness et al.⁴⁷ and 20 and 48% by Soudry et al.⁴³ were reported for the young and old patients, respectively. Hence, as per our analysis, the mean regional recurrence rate of OSCC in the young is 19.07 and 26.13% in old patients.

Locoregional Recurrence

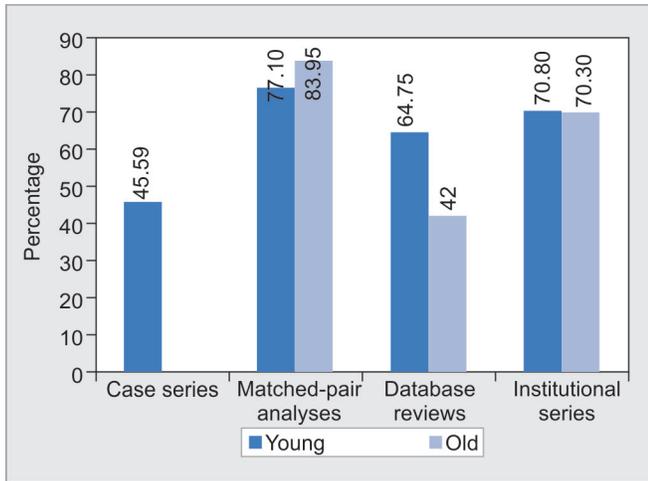
A locoregional failure of 66.70% among the young and 36% in old patients was observed by Fang et al.,⁵⁰ Veness et al.⁴⁷ noted 9.10% for the young and 3.50% for old patients. Liao et al.⁴⁸ reported 21.10% of the young and 26.40% of old patients. However, Soudry et al.⁴³ did not find any combined locoregional recurrence among young patients and noted 15% in old patients. Our analysis concluded that the mean rate of locoregional recurrence in the young is 24.23 and 20.23% in old ones.

Two-year Survival

The 2-year survival of 80% for the young and 75% for old patients was reported in the single institutional study by Veness et al.⁴⁷



Graph 1: Bar diagram showing the comparison of outcomes of different study designs



Graph 2: Bar diagram showing the comparison of mean survival rates of different study designs

Five-year Survival

Udeabor et al.⁴⁹ reported a 5-year survival of 66.20 and 57.60% for the young and old OSCC patients, respectively. Fifty-five percent of the young and 61% of the old patients included in the study by Soudry et al.⁴³ survived for 5 years. According to our review, the mean 5-year survival rate in young and old patients is 60.60 and 59.30%, respectively (Graph 2).

Distant Metastasis

Though none of the young patients with OSCC from the study by Hyam et al.⁴⁶ developed a metastatic disease later during the study, 2% of the patients included in the middle-aged group and 5% of the patients from the old-aged group demonstrated distant metastasis somewhere in the body. Fang et al.⁵⁰ also reported a distant metastatic disease in 7.50% of the old but none in the young. Veness et al.⁴⁷ and Liao et al.⁴⁸ showed it in 4.50 and 13.80% of the young and 1.40 and 4.50% of old patients, respectively. However, 60% of the included young patients by Soudry et al.⁴³ showed distant metastatic disease later whereas only 4% of the old patients developed distant metastasis. Hence, in the present review, the mean rate of distant metastasis of OSCC in the young is 15.66%, and in old patients, it is 4.48%.

Second Primary Tumor

Veness et al.⁴⁷ reported a second primary tumor in 9% of the included young and 7% of the old OSCC patients. It was seen in 6.75% of patients, all in the older group, in the study by Soudry et al.⁴³ The mean rate of emergence in the young and old patients with OSCC is 4.50 and 6.88%, respectively.

Cancer-related Deaths

Fang et al.⁵⁰ observed 33.3% of the young and 27.30% of old patients had died due to OSCC during the follow-up period. Liao et al.⁴⁸ and Udeabor et al.⁴⁹ reported the cancer-related deaths to be 25 and 34.20% among the young and 30 and 42.70% among old patients, respectively. On the contrary, Soudry et al.⁴³ documented a death rate of 45.45 and 27.02% among the young and old patients, respectively. According to the present review, the mean rate of cancer-related deaths in young OSCC patients is 34.49%, and that in the old is 31.55%.

DISCUSSION

OSCC is essentially believed to be a disease of middle-aged and old groups, with frequent association with tobacco use. However, recent literature documents an escalating incidence of OSCC among young individuals, further making the disease bizarre. Studies concerning the influence of age at the time of diagnosis on the treatment outcome of OSCC have produced inconsistent data with no definite conclusion about whether the prognosis in the younger age-group is poor, better, or similar to that of the older age-group. The primary objective of this systematic review was to compare different parameters such as prognosis, survival, local, and regional recurrence, distant metastasis, and cancer-related deaths among young and old individuals from the vast data available in the literature. Of the total case reports included, the maximum reported the prognosis to be worse for young patients. However, data from most of the included matched-pair analyses and institutional series suggest prognosis similar to that of old patients. On the other contrary, all the included database reports concluded that the prognosis of OSCC in young individuals is better than that of the old. A part of this discrepancy in the results can be attributed to the differences in the age cutoff of the young patient samples. Although most of the studies empirically considered <40 years, many of them have considered <20, <30, <35, <40, and <45 as the age limit for younger patient groups. Hence, it is quite difficult to achieve dependable results regarding the prognosis of OSCC when comparing these heterogeneous data owing to this inconsistency as to what age is to be considered as the standard limit for contemplating a patient as young.

Several authors attempted to analyze the prognosis and treatment results of OSCC in young patients through case series reports but failed to compare them with the older counterpart. Overall survival of 75% was observed among young patients who were treated for OSCC in a retrospective study by Martin-Granizo et al.²⁰ A similar survival result was observed in the study by McGregor et al.⁹; however, of the included young cases of OSCC, 3.7% of young individuals with OSCC of the tongue developed a second primary lesion later in life. This result is inconsistent with that of Amsterdam et al.⁸ who reported a second primary lesion later on after treatment in 25% of young patients with OSCC at sites other than the tongue. The study by Amsterdam et al.⁸ reports a 5-year survival of young patients with tongue cancer to be 14.28% in contrast to 75% for those with cancer at any other oral site. Also, the number of young patients with tongue cancer showed a significantly higher rate of distant metastasis when compared to young individuals with squamous cell carcinoma (SCC) of some other oral site (71 and 25%, respectively). A lot of evidence in the literature have shown that tongue OSCC behaves as a different entity. These results suggest that tongue cancer in a young individual can be suspected to be more aggressive as compared to that of any other oral site and demands prompt and extensive treatment with consistent and timely follow-up.

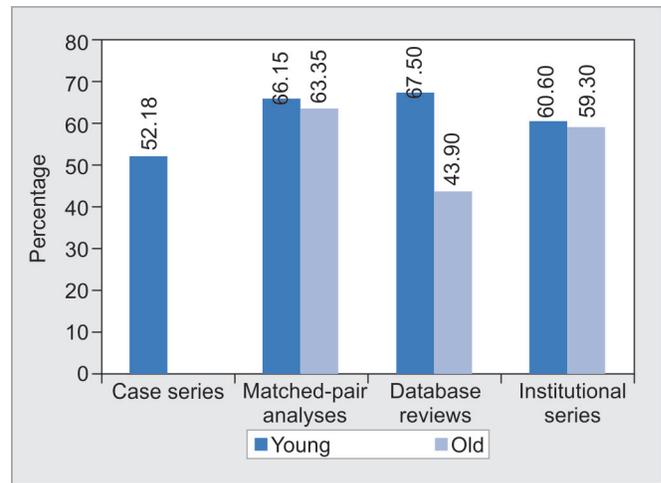
Many authors attempted to compare the prognosis and treatment consequences of OSCC in young and old patients through matched-pair analyses. The majority of the results demonstrated a similar prognosis of OSCC in young and old patient groups emphasizing the treatment approach and intensity to be similar for all the cases, whether young or old. Interestingly, one of the matched-pair analyses by Vargas et al.³⁷ considered only young women with tongue OSCC and compared the results with older controls that included both males and females. The results showed a

worse prognosis for young women with tongue cancer as compared to the older group, with a considerably high locoregional recurrence rate (young patients: 65%, old patients: 41%) and a somewhat low overall survival (young patients: 65%, old patients: 76%). Though the study does not signify any relationship between gender and prognosis of OSCC, as the included young females were tobacco nonusers, it can be believed that these young patients are somehow genetically predisposed to acquiring the malignancy. Keegan et al.³⁰ match-paired 989 young patients with oral and oropharynx cancer with an old group and found the 5-year survival rates for the younger group to be higher than the older group, 80.7 and 62%, respectively, suggesting the prognosis to be better for younger patients.

All the five database reviews concluded the prognosis of OSCC to be better for young individuals as compared to the old. In the database review by Schantz et al.³⁴ that compared the incidence trends of HNSCC in young Americans with a special analysis for tongue cancer, the study was performed for distinct periods: 1973 to 1984 and 1985 to 1997. The study results demonstrated an overall survival that was considerably better for the young age-group as compared to very low survival for the middle- and old-aged groups during both the study periods. However, 5-year survival improved more than 20% in young patients with regional and metastatic disease. The improved survival rate and early-stage disease were not observed in the young black population that showed poor prognosis and high metastatic cancer-related death. This implies the likelihood that various socioeconomic strata are contributing to the disclosure of a conspicuously diverse disease process among young individuals.

We observed that the rate of local recurrence and distant metastasis of the tumor is more in young individuals with OSCC than in the old. Fang et al.⁵⁰ reported the local recurrence rate to be 60 and 11.18% for the young and old OSCC patients, respectively. Soudry et al.⁴³ found a higher rate of distant metastasis in young patients as compared to the old with a rate of about 60% among the young and 4% among old patients, in agreement with the high rate of metastasis in the younger groups of Liao et al.⁴⁸ and Jeon et al.³¹ Moreover, a high percentage of these recurrent young patients died of the disease. This could be accredited to two reasons: a delay in diagnosis owing to a lower index of clinical suspicion of OSCC in younger patients or a more aggressive age-related biologic behavior of the malignancy. On histopathological examination of tumor samples of young patients, Soudry et al.⁴³ identified a significantly higher rate of perineural invasion. This could explain much about the distinctive and aggressive age-related biologic behavior of OSCC in young patients as the perineural invasion is associated with a high risk of tumor metastasis, local recurrence, and decreased survival. Recently, a new specific histological pattern is identified to be consistent with an increased incidence of nodal and distant metastasis in young patients. Small groups or cords of cells, as well as single cells disassociated from the rest of the tumor mass, are noted in the margins of many young patients.

Several studies in the literature have shown that OSCC in young individuals behaves as a distinctive entity. Byers¹⁶ emphasizes that a more virulent behavior and poorer prognosis can be attributed to a more anaplastic tendency of OSCC among young individuals. A relatively high expression of p53 without mutation in exon 5-9 was observed in young OSCC nonsmoker patients by Ligen et al.⁵³ Schantz et al.⁵⁴ accounted for a greater fragility of chromosome in



Graph 3: Bar diagram showing the comparison of mean 5-year survival rates of different study designs

lymphocytes from young patients with HNSCC following treatment with bleomycin. Polymorphism of cyclin D1 gene (CCND1) was found to be allied with the early onset of HNSCC, and contributed to the propensity of its development, particularly in young nonsmokers and nondrinkers in a case-control study by Zheng et al.⁵⁵ Low levels of EGFR expression were associated with a lower recurrence rate in young patients, and those with high levels of expression had adverse prognosis.⁵⁶

CONCLUSION

- The overall outcome of the systematic review of the case series support that the occurrence of OSCC in young patients comes with a poor prognosis and hence should be considered as an aggressive disease in them.
- On the contrary, the results from the included matched-pair analyses suggest no significant difference in the prognosis of the young and old OSCC patients.
- All the databases that are included in this systematic review favored a better prognosis of OSCC in young patients than that in old ones.
- A similar kind of prognosis for young and old patients with OSCC can be inferred from the systematic review of the institutional series considered in this article.
- The mean overall survival rate was found to be better for young OSCC patients in the database and institutional review whereas worse in the matched-pair analyses (Graph 2).
- The mean 5-year survival rate was found to be more in young individuals with OSCC in matched-pair analyses, database reviews, and institutional series as compared to older OSCC patients (Graph 3).

Thus, from the present review, it is difficult to comment on the prognosis of OSCC patients in young vs old as all the four subgroups are heterogeneous with different reported outcomes. More future follow-up studies are required to comment on the same.

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(Annexure: Sheet 1)

Sr. No.	Author	Year	Duration	Country	Site	Cases (Young)	Controls (Old)	Age limit	Study design	Outcome
1	Venables CW et al. ¹⁵	1967	1925-1966	UK	Tongue	13		<30	Case series	Worse
2	Byers RM ¹⁶	1975	1956-1973	US	Tongue	11	407	<30	Case series	Worse
3	Amsterdam JT et al. ⁸	1982	1954-1979	US	Group A: Tongue; Group B: other oral site	12 (8+4)		<35	Case series	Worse
4	McGregor GI et al. ⁹	1983	1944-1982	Canada	Tongue, Other sites	36 (27+9)		<40	Case series	Better
5	Newman AN et al. ¹⁰	1983		US	Tongue	13 (1 refused treatment)		<30	Case series	Similar
6	Son YH et al. ¹¹	1985	1958-1980	US	Oral cavity, Oropharynx	26 (24+3)		<40	Case series	Worse
7	McGregor AD et al. ¹²	1987		UK	Oral cavity	13		<40	Case series	Similar
8	Benninger MS et al. ¹³	1988	1977-1985	US	Head & Neck (Oral cavity)	41 (9)		<40	Case series	Worse
9	Cusumano RJ et al. ¹⁴	1988	1961-1984	US	Oral cavity, oropharynx	23 (14+9)		<40	Case series	Worse
10	Sarkaria JN et al. ¹⁸	1994	1971-1991	US	Tongue	6		<40	Case series	Worse
11	Atula S et al. ¹⁹	1996	1980-1989	Finland	Tongue	34		<40	Case series	Similar
12	Martin-Granizo R et al. ²⁰	1997	1979-1994	Spain	Oral cavity, oropharynx	24 (20+4)		<40	Case series	Similar
13	Hart AK et al. ²¹	1999	1975-1996	US	Oral cavity, oropharynx	13 (9+4)	7 (5+2)	<45	Case series	Similar
14	Iype EM et al. ¹⁷	2001	1982-1996	India	Tongue	115		<35	Case series	Similar

Oral Cancer: Young vs Old

Overall survival	Overall recurrence	Local recurrence	Regional recurrence	Locoregional recurrence	2-year survival	3-year survival	5-year survival	Distant metastasis	Second primary lesion	Cancer-related deaths
46.15%		7.69%	46%	30.77%	61.53%	46.15%	30.76%	7.69%		53.84%
45%			55%	18%	45%			18.18%		55%
Group A: 43%; Group B: 75%; Combined: 55%		Group A: 29%; Group B: 0; Combined: 18%	Group A: 71%; Group B: 25%; Combined: 55%		Group A: 57%; Group B: 75%; Combined: 75%		Group A: 14.28%; Group B: 75%; Combined: 36%	Group A: 71%; Group B: 25%; Combined: 55%	Group A: 0; Group B: 25%; Combined: 9%	Group A: 50.00%; Group B: 25%; Combined: 41.66%
Total: 75%; Tounge: T1= 93.33%; T2= 70%; T4=100%; Other: 55.55%			25%						3.70% (Tongue cases)	Total: 19.44%; Tongue: T1=6.66%; T2=20%; T3=100%; T4=0; Other: 33.33%
42%		8.33%	25%	8.33%						58.33%
16.66%	16.66%								4.16%	83.33%
		69.23%			31%	15%				69.23%
22.20%		88.80%					21.00%			77.77%
		15.38%	15.38%	15.38%			Stage I, II: 100%; Stage III, IV: 16.6%			
33.30%		16.60%	33.30%	33.30%	33.30%	33.30%				66.60%
							70.60%			35.30%
75% (Stage 1 and 2: 85.7%, Stage 3 and 4: 50%)	20% (Stage 1 and 2: 10%, Stage 3 and 4: 10%)								15.00%	
		11.11%		11.11%	66.66%	55.55%	55.55%			
		40.60%	15.60%	34.40%		91%	87.00%	6.30%		

(Annexure: Sheet 2)

Sr. No.	Author	Year	Duration	Country	Site	Cases (Young)	Controls (Old)	Age limit	Study design	Outcome	Type of matched survival analysis
1	Lipkin A et al. ³³	1985	1964-1983	US	Oral cavity, oropharynx, larynx	39	39	<40	Matched Control (sx, si, st)	Similar	
2	Schantz SP et al. ³⁴	1988			Head & Neck (oral cavity)	83 (36)	83 (36)	<40	Matched Control (sx, si, st, y)	Worse	chi-square test, kaplan-meier, log rank analysis
3	Kuriakose M et al. ³²	1992	1988-1990	India	Oral cavity	37	37	<35	Matched Control	Worse	Chi-square test
4	Friedlander PA et al. ³⁵	1998		US	Tongue	36	36	<40	Matched Control (sx, st, y)	Similar	
5	Verschuur HP et al. ³⁶	1999	1958-1992	Canada	Head & Neck (oral cavity)	185 (80)	185 (80)	<40	Matched Control (sx, si, y)	Similar	retrospective cohort study, cox proportional hazard, kaplan-meier
6	Vargas H et al. ³⁷	2000		US	Tongue	17 (only females)	17 (both males and females)	<40	Matched Control (st)	Worse (women)	
7	Popovtzer A et al. ²²	2004	1983-2001	Israel	Tongue	16	32	<45	Matched-pair analysis	Similar	chi-square test, log-rank test
8	Pytynia KB et al. ²³	2004	1995-2001		Head & Neck (oral cavity)	31 (13)	62 (26)	<40	Matched Control (sx, r, si, st, tx)	Similar	cox proportional hazard, kaplan-meier, log rank analysis
9	Sasaki T et al. ²⁴	2005	1990-1999	England	Oral cavity	35	110	<40	Matched Control (random sample)	Similar	Chi-square test, ANOVA
10	Garavello W et al. ²⁵	2007	1981-1998	Italy	Tongue	46	92	<40	Matched Control (sx, si, st)	Worse	fisher exact test, kaplan & meier, log-rank test
11	Lee CC et al. ²⁶	2007	1999-2005	Taiwan	Tongue	20	20	<45	Matched Control (sx, st)	Better	kaplan-meier product limit method, log rank test
12	Ho HC et al. ²⁷	2008	1999-2005	Taiwan	Oral cavity	28	56	<45	Matched Control (sx, si, st)	Better	cox proportional hazard models, Kaplan-Meier, log-rank test
13	Kaminagakura E et al. ²⁸	2010		Brasil	Oral cavity	125	250	<41	Matched-pair analysis	Similar	

<i>Overall survival (P)</i>	<i>Matched survival analysis</i>	<i>Overall recurrence</i>	<i>Local recurrence</i>	<i>Regional recurrence</i>	<i>Locoregional recurrence</i>	<i>5-year survival</i>	<i>Distant metastasis</i>	<i>Second primary lesions</i>	<i>Cancer-related deaths</i>
			Young:14.45%, Old:9.63%	Young:13.25%, Old:9.63%		Young: 66%, Old:86%	Young:8.43%, Old:8.43%	Young:3.8%, Old:6.8%	
Young:89.2%, Old:91.9%									Young: 10.8%, Old:2.7%
			Young:28%, Old:14%	Young:25%, Old:17%	Young:44%, Old:22%	Young: 62%, Old:69%			
			Young:36.21%, Old:43.2%	Young:28.1%, Old: 27.6%		Young: 68%, Old:49%	Young:8.1%, Old:6.5%	Young:8.1%, Old:18.4%	Young: 41.6%, Old:72.4%
Young:65%, Old:76%		Young:65%, Old:41%							
		Young:58%, Old:57.1%							Young: 42%, Old:36%
		Young: 19.4%; Old:16.1%							Young: 25.8%
~	young: 34%; old: 58%	young: 74%; old: 51%	young: 39%; old: 24%	young: 26%; old: 25%		~	young: 9%; old: 2%	~	younger: 50%; older: 34%
0.013 (KM estimate & log-rank test)	younger: 55±3m; older: 36±5m	~	younger: 5%; older: 25%	younger: 15%; older: 30%		~	younger: none; older: 10%	~	~
0.024 (KM estimate & log-rank test)		~	younger: 21.40%; older: 39.3%	younger: 17.8%; older: 21.4%		Young: 78.2%, Old:44.1%	younger: 10.7%; older: 16.1%		Young: 64.3%, Old:5.4%

(Annexure: Sheet 2) Continued

14	Park JO et al. ²⁹	2010	1994-2004	Korea	Tongue	23	62	<45	Stage-matched comparative analysis	Worse	Chi-square test, Kaplan-meier, Fisher's test, log-rank test
15	Keegan TH et al. ³⁰	2016	2002-2006	USA	Oral cavity and pharynx	989		15-39	Matched-pair analysis	Better	
16	Jeon JH et al. ³¹	2017	2001-2011	South Korea	Tongue	23	94	<40	Matched-pair analysis	Worse	chi-square analyses, Kaplan-Meier method and log-rank tests.

(Annexure: Sheet 3)

Sr. No.	Author	Year	Duration	Country	Site	Cases (Young)	Controls (Old)	Age limit	Study design	Outcome
1	Lacy PD et al. ⁴⁰	2000	1980-1991	US	Head & Neck	40	Middle-aged: 566, Old: 424	<40	Database review (Washington University Cancer Registry)	Better
3	Annertz K et al. ⁴¹	2002	1960-1994	Scandinavian countries	Tongue	276	4748	<40	Database Review (Scandinavian Cancer Registry)	Better
2	Funk GF et al. ³⁹	2002	1985-1996	US	Oral cavity	1039	Middle aged: 26181, Old: 24757	<35	Database Review (National Cancer Database)	Better
4	Schantz Sp et al. ⁴²	2002	1973-1997	US	Head & Neck (Tongue)	1973-1984: 204, 1985-1997: 413	1973-1984: Middle-aged: 2886, Old: 3485; 1985-1997: Middle-aged: 2212, Old: 3348	<40	Database Review (SEER 1973-1997)	Better
5	Morris LG et al. ³⁶	2010	1973-2006	US	Oral cavity	54	22162	<20	Database review {National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) registry 1973-2006}	better



Oral Cancer: Young vs Old

			Young: 21% , Old: 18.4%	Young: 47% , Old: 11.2%				Young: 65.6%, Old: 71%	Young: 0, Old: 16%
						Young: 80.7%, Old:62%			
			Young:0, Old:2.1%	Young:4.3%, Old:9.6%	Young:26%, Old:11%	Young: 42%, Old:70%	Young:26%, Old:2.1%		

<i>Overall survival</i>	<i>Over-all recurrence</i>	<i>Local recurrence</i>	<i>Regional recurrence</i>	<i>Loco-regional recurrence</i>	<i>2-year survival</i>	<i>3-year survival</i>	<i>5-year survival</i>	<i>Distant metastasis</i>	<i>Second primary lesion</i>	<i>Cancer-related deaths</i>
							Young: 65%, Middle- aged: 52%, Old: 38%			
							Young: 66%, Middle: 48%, Old: 43%%			
					Young: 72.3%, Middle: 67.4%, Old: 62.5%	Young: 67.5%, Middle: 59.7%, Old: 56%	Young: 63.7%, Middle: 51%, Old: 47.6%			
1973-1984: Young: 58.9%, Middle- aged: 43.2%, Old: 38.2%; 1985-1997: Young: 70.6%, Middle-aged: 49.8%, Old: 45.8%										
							Young: 75.3%, Old: 47.1%			

(Annexure: Sheet 4)

Sr. No.	Author	Year	Duration	Country	Site	Cases (Young)	Controls (Old)	Age limit	Study design	Outcome
1	Vermund H et al. ⁴⁴	1982	1958-1972	Norway & US	Tongue	16	384	<40	Institutional series	Better
2	von Doersten PG et al. ⁴⁵	1995	1981-1988	US	Head & Neck (oral cavity)	155 (23)	132	<40	Institutional series	Similar
3	Siegelmann-Danieli et al. ⁵¹	1998		US	Tongue	30	57	<45	Institutional series	Similar
4	Hyam DM et al. ⁴⁶	2003	1979-2000	Australia	Tongue	15	Middle age: 48, Old age: 60	<40	Institutional series	Better
5	Veness MJ et al. ⁴³	2003	1980-2000	Australia	Tongue	22	142	<40	Institutional series	Similar
6	Liao CT et al. ⁴⁸	2006	1996-2003	Taiwan	Tongue	76	220	<40	Institutional series	Similar
7	Soudry E et al. ⁴³	2010	1992-2007	Israel	Tongue	11	74	<30	Institutional series	Similar
8	Udeabor SE et al. ⁴⁰	2012	1980-1999	Germany	Oral cavity, oropharynx	38 (Only oral cavity)	939	<40	Institutional series	Better
9	Chang TS et al. ⁴³	2013	2004-2005	Taiwan	Oral cavity	608	Middle-aged: 1416, Old-aged: 315	<45		Similar
10	van Monsjou HS et al. ⁶	2013	1977-2008	Netherland	Oral cavity, oropharynx	54	1708	<40	Institutional medical records (1977-2008)	Better
11	Fang QG et al. ⁵⁰	2014	2005-2011	China	Tongue	15	161	<40	Institutional medical records (1997 to 2011)	Similar

Over-all survival	Over-all recurrence	Local recurrence	Regional recurrence	Locoregional recurrence	2-year survival	3-year survival	5-year survival	Distant metastasis	Second primary lesion	Cancer-related deaths
		Young: 13%, Middle-aged: 21%, Old: 27%	Young: 27%, Middle-aged: 6%, Old: 12%					Young: 0, Middle-aged: 2%, Old: 5%		
		Young: 9.1%, Old: 7.7%	Young: 22.7%, Old: 19.7%	Young: 9.1%, Old: 3.5%	Young: 80%, Old: 75%			Young: 4.5%, Old: 1.4%	Young: 9%, Old: 7%	
Young: 75%, Old: 68%				Young: 21.1%, Old: 26.4%				Young: 13.8%, Old: 4.5%		Young: 25%, Old: 30%
		Young: 20%, Old: 30%	Young: 20%, Old: 48%	Young: 0, Old: 15			Young: 55%, Old: 61%	Young: 60%, Old: 4%	Young: 0, Old: 6.75%	Young: 45.45%, Old: 27.02%
							Young: 66.2%, Old: 57.6%			Young: 34.2%, Old: 42.7%
Young: 66.6%, Old: 72.6%		Young: 60%, Old: 11.18%	Young: 6.6%, Old: 24.8%	Young: 66.7%, Old: 36%				Young: 0, Old: 7.5%		Young: 33.3%, Old: 27.3%