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Review Paper
Head and Neck Oncology

What has the National Cancer Database taught us about oral cavity squamous cell carcinoma?

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Abstract. The wealth of data in the National Cancer Database (NCDB) has allowed numerous studies investigating patient, disease, and treatment-related factors in oral cavity squamous cell carcinoma (OCSCC); however, to date, no summation of these studies has been performed. The aim of this study was to provide a concise review of the NCDB studies on OCSCC, with the hopes of providing a framework for future, novel studies aimed at enhancing our understanding of clinical parameters related to OCSCC. Two databases were searched, and 27 studies published between 2002 and 2020 were included. The average sample size was 13,776 patients (range 356–50,896 patients). Four areas of research focus were identified: demographic and socioeconomic status, diagnosis, prognosis, and treatment. This review highlights the impact of age, sex, ethnicity, and socioeconomic status on the prognosis and management of OCSCC, describes the prognostic factors, and details the modalities and indications for neck dissection and adjuvant therapy in OCSCC. In conclusion, the NCDB is a very valuable resource for clinicians and researchers involved in the management of OCSCC, offering an incomparable perspective on a large dataset of patients. Future developments regarding hospital information management, review of data accuracy and completeness, and wider accessibility will help clinicians to improve the care of patients affected by OCSCC.

Key words: oral cavity squamous cell carcinoma; oral cancer; database; socioeconomic status; prognostic factors; neck dissection; radiation therapy.

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Oral cavity squamous cell carcinoma (OCSCC) is the sixth most common cancer in the world[1]. The American Cancer Society estimated that 35,310 individuals would be diagnosed with OCSCC in the United States in 2020 and 7110 would die from this malignancy[2]. Today, the reported 5-year survival for OCSCC is around 64%[3], and there have been no significant improvements in survival over the past few decades[1]. Tobacco and alcohol consumption are still the main etiological risk factors for OCSCC[4]. Surgical resection remains the optimal first-line treatment for OCSCC, with radiotherapy

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and chemotherapy serving as adjunctive measures aimed at improving overall survival and loco-regional control in select cases.

Today, head and neck cancer specialists have robust scientific data from the National Cancer Database (NCDB), which is a cancer registry organized by the American Cancer Society and the American College of Surgeons that provides hospital-based case data from over 1500 Commission on Cancer-accredited hospitals[5]. NCDB data represent more than 70% of newly diagnosed cancer cases within the United States[5]. Large cancer databases such as the NCDB allow investigators the opportunity to examine a myriad of factors related to oncological outcomes in malignancies including OCSCC[6,7].

The wealth of data in the NCDB has allowed numerous studies investigating patient, disease, and treatment-related factors in OCSCC; however, to date, no summation of these studies has been performed. Therefore, the aim of this study was to provide a concise review of the NCDB studies on OCSCC, with the hopes of providing a framework for future, novel studies aimed at enhancing our understanding of clinical parameters related to OCSCC.

Materials and methods

A search using the abstract and citation databases PubMed and Scopus was performed to identify NCDB articles on OCSCC. Two combinations of search terms were utilized: ''Oral cancer'' AND ''NCDB''; ''Oral squamous cell carcinoma'' AND ''NCDB''. No time limit or language restriction was applied for inclusion. All NCDB studies for which the principle aim focused on OCSCC were included. Studies dealing with oral cancers other than squamous cell carcinoma (SCC) (e.g., minor salivary gland malignancies) or head and neck carcinomas located in non-oral cavity anatomical sites were excluded. Three of the review authors separately determined the main bullet point of each included article. They then compared their bullet points, and in the case of a discrepancy, discussions were held until a consensus was reached. No statistical analyses were attempted because the different studies were based on the same sample of patients included within the NCDB.

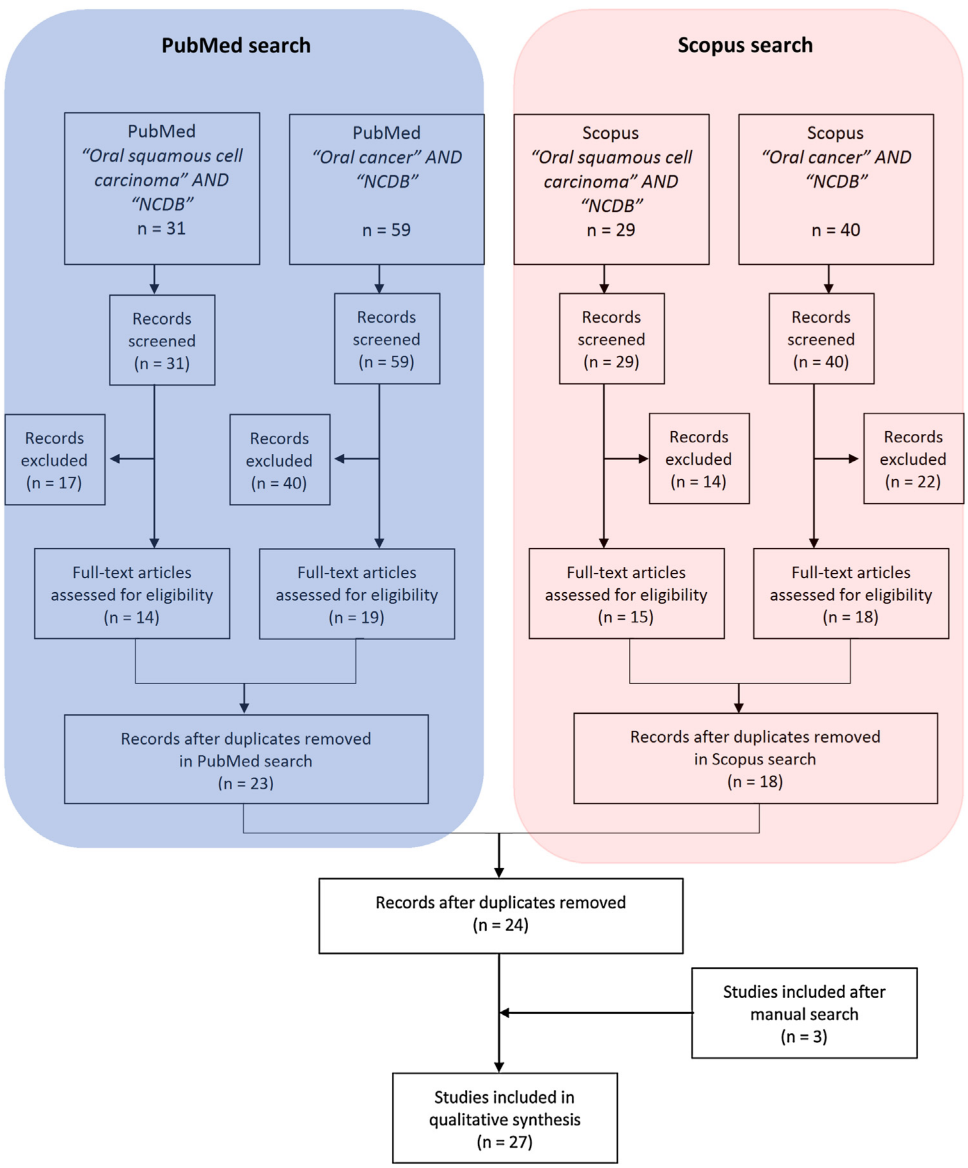

Fig. 1. Flow chart of the study selection.

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Table 1. Characteristics of the studies included in the review.

Study	Year	Journal	Research focus	Cancer subtype	Sample size	Studied years	First aim
Oliver et al.[8]	2019	Head Neck	DSE	OC	22,930	2004–2015	To determine the influence of age on survival using a propensity score matched analysis controlling for all available prognostic factors; secondary aim was to analyze patterns of care and determine whether management strategies currently differ by patient age
Li et al.[9]	2018	Cancers Head Neck	DSE	OC and OP	30,707 (9080 OCSCC)	2010–2014	To determine if sex is associated with overall survival in patients with high-risk HPV-positive and HPV-negative SCCs in the oropharynx and oral cavity sites
Funk et al.[10]	2002	Head Neck	DSE	OC	58,976 (50,896 OCSCC)	1985–1996	To perform a detailed analysis of oral cavity cancer
Lewis et al.[11]	2018	Head Neck	DSE	OC	25,357	2004–2013	To assess the disparities in treatment selection for OCSCC
Shin et al.[12]	2018	Int J Oral Maxillofac Surg	DSE	OC	46,373	2004–2013	To determine the influence of insurance status on treatment and outcomes in oral cavity cancer
Bur et al.[13]	2019	Oral Oncol	Diagnosis	OC T1–2	1971	2007–2013	To develop and validate an algorithm to predict occult nodal metastasis in clinically node-negative OCSCC using machine learning
Schwam and Judson[14]	2016	Oral Oncol	Prognosis	OC and OP	13,655	1998–2006	To quantify improvement in survival of OCSCC and to determine factors associated with survival in the United States
Namin et al.[6]	2020	Otolaryngol Head Neck Surg	Prognosis	OC T4a	1559	2004–2015	To determine if tumor size, subsite, and adjuvant radiation therapy are associated with overall survival in patients with pT4aN0 OCSCC who have undergone mandibulectomy with negative surgical margins
Cheraghlou et al.[15]	2018	Laryngoscope	Prognosis	OC	356	2004–2012	To outline the natural history, with a secondary aim of identifying predictors of treatment refusal
Ho et al.[16]	2017	J Clin Oncol	Prognosis	OC	14,554	2004–2013	To investigate the independent impact of numerical metastatic lymph node burden on survival
Zhan et al.[17]	2018	Head Neck	Prognosis	OC	2623	1998–2012	To identify nodal predictor in cT1N0
Kılıç et al.[33]	2018	Head Neck	Prognosis	OC	9110	2004–2013	To examine the frequency and survival implications of clinicopathological stage discrepancy in OCSCC
Luryi et al.[18]	2016	Head Neck	Prognosis	OC	21,681	2003–2011	To evaluate rates of 30-day hospital readmission and mortality after surgery for oral cavity
Rubin et al.[19]	2017	Laryngoscope	Treatment	OC	32,510	1998–2011	To determine whether facility type affects overall survival in patients with oral cavity cancer
Ellis et al.[20]	2018	Otolaryngol Head Neck Surg	Treatment	OC stage I–II	20,779	2004–2014	To determine the effect of primary surgery vs radiotherapy on overall survival in patients with early stage OCSCC
Spiotto et al.[21]	2017	JAMA Otolaryngol Head Neck Surg	Treatment	OC stage III–IVA	6900	2004–2012	To compare the differences in survival between patients with locally advanced OCSCC treated with surgery and postoperative radiotherapy or chemoradiotherapy
Fujiwara et al.[22]	2017	Oral Oncol	Treatment	OC	23,459	1998–2011	To identify predictors of choice of treatment modality for oral cavity malignancies
Luryi et al.[23]	2014	Otolaryngol Head Neck Surg	Treatment	OC stage I–II	20,602	1998–2011	To evaluate the incidence of positive surgical margins in early oral cavity cancer and identify patient, tumor, and system factors associated with their occurrence
Kuo et al.[24]	2016	Cancer	Treatment	OC	13,143	1998–2006	To identify optimal thresholds in elective and therapeutic neck dissection for oral cavity cancers

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Table 1 (*Continued*)

Study	Year	Journal	Research focus	Cancer subtype	Sample size	Studied years	First aim
Zenga et al.[25]	2019	Oral Oncol	Treatment	OC T1–2	4771	2004–2015	To determine the effects of nodal yield on survival in early stage OCSCC in the context of primary tumor DOI
Tsai et al.[26]	2017	JAMA Otolaryngol Head Neck Surg	Treatment	OC cN0	7811	2004–2012	To evaluate the survival impact of lymph node count in cN0 patients with OCSCC
Mann et al.[27]	2019	Cureus	Treatment	Tongue T1–2	939	2006–2013	To evaluate the potential benefit of postoperative radiotherapy in pT1–2N0 (stage I and II) oral tongue cancers with a DOI > 4 mm
Chen et al.[28]	2016	JAMA Otolaryngol Head Neck Surg	Treatment	OC and OP pT1–2N1	2257 (1467 OCSCC)	2004–2013	To examine the use and outcomes of postoperative radiotherapy for N1 oropharyngeal and oral cavity SCC
Rubin et al.[29]	2018	Otolaryngol Head Neck Surg	Treatment	Tongue pT2N0	934	2004–2013	To determine if adjuvant radiation therapy for patients with pT2N0 oral cavity tongue cancer affects overall survival
Fujiwara et al.[30]	2017	Head Neck	Treatment	OC	4868	1998–2011	To determine the impact of delays on overall survival
Amini et al.[31]	2019	Head Neck	Treatment	OC	10,832	2004–2013	To evaluate whether postoperative radiotherapy at the same facility as surgery portends to better survival outcomes compared to postoperative radiotherapy given at a different facility
Spiotto et al.[32]	2017	Head Neck	Treatment	Tongue	2803	2004–2012	To compare the survival outcomes for surgery + postoperative radiotherapy vs surgery + postoperative chemoradiation in patients with oral tongue cancers with intermediate-risk pathological features

DOI, depth of invasion; DSE, demographic and socioeconomic; HPV, human papillomavirus; OC, oral cavity; OCSCC, oral cavity squamous cell carcinoma; OP, oropharynx; SCC, squamous cell carcinoma.

Results

The query search in PubMed and Scopus resulted in 159 articles, of which 93 were excluded because they did not match with the topic (Fig. 1). After the removal of duplicates and adding three studies identified in a manual search, a total of 27 studies were included, published between 2002 and 2020 (Table 1)[6,8–33]. The greatest number of articles were published in *Head and Neck* (9/27), followed by *Oral Oncology* (4/27) and *Otolaryngology–Head and Neck Surgery* (4/27) (Fig. 2). The average sample size was 13,776 patients (range 356–50,896 patients). The four areas of research focus were demographic and socioeconomic status, diagnosis, prognosis, and treatment (Fig. 3), forming the basis by which the studies were organized.

Impact of demographic and socioeconomic status

Patients under 40 years old with oral tongue SCC had a significant reduction in the risk of mortality (hazard ratio (HR) 0.59, 95% confidence interval (CI) 0.55–0.65; $P < 0.001$) and a 9% higher 5-year survival (77.1% vs 68.2%, $P < 0.001$) than patients between 40 and 70 years old[8]. Female patients had a better survival in OCSCC than male patients in both non-human papillomavirus (HPV) and HPV-associated cancers ($P = 0.049$ and $P < 0.001$, respectively)[9]. African American patients diagnosed with OCSCC had a significantly lower overall survival than patients of other ethnicities[10–12], regardless of their income[10]. African American patients were more likely not to receive surgery or to refuse surgery than patients of other ethnicities, even if surgery was recommended for the treatment of an OCSCC[11]. Having private medical insurance was a significant prognosticator for improved overall survival when compared to being uninsured, on Medicaid, or on Medicare[12].

Diagnostics

Machine learning improved the prediction of pathological nodal metastasis compared to depth of invasion (DOI) in patients with clinical T1–2N0 OCSCC[13]. No other study utilized the NCDB for a diagnostic-based study.

Prognostic variables

Patients with OCSCC at early (stages I and II) and late stages (stages III and IV) had

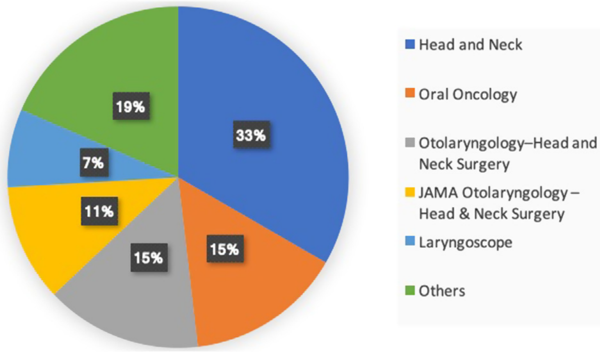

Fig. 2. Distribution by journal of the publications focusing on oral squamous cell carcinoma based on the NCDB.

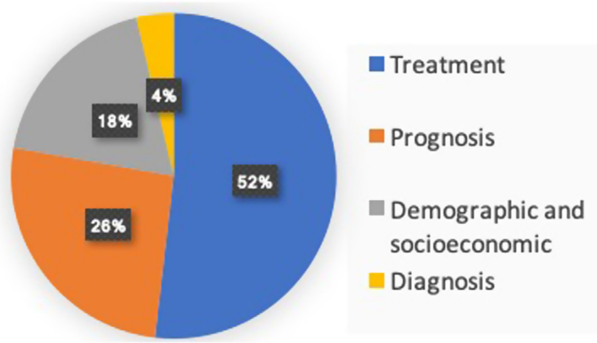

Fig. 3. Distribution by area of research focus of the publications on oral squamous cell carcinoma based on the NCDB.

improvements of 36.2% and 16.0% in 3-year overall survival, respectively, in 2004–2006 compared to 1998–2003[14]. Patients who were recommended to have surgery and refused treatment had 5-year survival rates that ranged from 12.6% for those with stage IV disease to 31.1% for those with early-stage disease[15]. SCC of the oral tongue and SCC of the floor of the mouth were associated with worse overall survival compared to SCC at other anatomical subsites in pT4aN0 OCSCC[6]. While the number of metastatic nodes in OCSCC was a critical predictor of mortality, other features such as lymph node size and contralaterality were not determined to be prognostic for survival on multivariable analysis[16]. The incidence of occult nodal disease in cT1N0 OCSCC was 15.1% overall and was higher in females (16.7%) than in males (13.9%) ($P = 0.049$). Compared to well-differentiated tumors (5.9%), the incidence of occult nodal disease was higher in moderately differentiated (17.4%) and poorly differentiated tumors (28.5%) ($P < 0.001$)[17].

Pathological upstaging occurred in 19.9% of the OCSCC cases (cII and cIII to pIVA being the most common upstaging), resulting in a poorer prognosis in all stages (except IVB), and was associated with advanced age, higher tumor grade, and increased time to treatment. Downstaging occurred in 12.8%, with cII to pI being the most common downstaging event. Downstaging was associated with increased survival at stages cII, cIII, and cIVA, but not at stages cIVB and cIVC[18].

Hospital readmission occurred in 3.5% of surgically treated OCSCC and was associated with male sex, stage T3 or T4 disease, neck dissection, and radical surgery[18]. Likewise, the incidence of 30-day mortality following OCSCC surgery was identified as 1% and was associated with age ≥65 years, comorbidity index ≥1, and stages T2, T3, and T4[18].

Impact of various treatment modalities

Patients treated for OCSCC at academic centers were more likely to receive surgical treatment, and had a greater 5-year overall survival compared to those treated within community cancer programs and comprehensive community cancer programs[19]. In early stage OCSCC (stages I and II), primary radiotherapy was associated with an increased risk of mortality compared to primary surgery (adjusted HR 1.97, 99% CI 1.74–2.22; $P < 0.001$)[20]. Compared with adjuvant radiotherapy, postoperative chemoradiotherapy was associated with improved survival for locally advanced OCSCC, especially in T3 to T4a disease and patients with two or more involved metastatic lymph nodes[21]. In all-stage OCSCC, non-surgical treatment was associated with decreased overall survival compared to primary surgery resection (HR 2.02; $P < 0.001$)[22]. Positive margins were present in 7.5% of cases, and associated with stage II disease, high tumor grade, floor of mouth, buccal mucosa, or retromolar trigone subsites, and treatment at non-academic facilities or facilities reporting less than 20 cases per year[23].

More extensive neck dissection (≥16 lymph nodes in cN0, ≥26 lymph nodes in cN+) was associated with better survival in OCSCC[24]. In OCSCC with early T-stage and clinically negative nodes, neck dissection with a nodal yield of 18 or more improved overall survival as compared with observation of the neck, in both thick (DOI ≥ 4 mm) and thin (DOI < 4 mm) tumors[25]. On multivariable analysis, patients with clinically negative necks with >24 nodes resected had longer overall survival compared to those who had ≤24 nodes resected (HR 0.82, 95% CI 0.75–0.88; $P < 0.001$)[26].

In pT1–2N0 (stage I and II) oral tongue cancers, the addition of elective neck dissection improved overall survival for DOI > 4 mm ($P = 0.010$), but not for DOI ≤4 mm ($P = 0.128$). The addition of postoperative radiotherapy did not improve overall survival with tumor DOI ≤4 mm ($P = 0.634$) or >4 mm ($P = 0.816$)[27].

Postoperative radiotherapy was associated with improved survival in patients with pN1 OCSCC (HR 0.76, 95% CI 0.63–0.92; $P < 0.001$), especially in those younger than 70 years or those with pT2 disease[28]. An overall survival benefit was not demonstrated for patients who received postoperative radiation therapy versus surgery alone for pT2N0 oral cavity tongue SCC, irrespective of depth of tumor invasion[29]. Radiation gaps and prolonged radiotherapy durations were significantly associated with decreased overall survival in OCSCC (HR 1.21; $P = 0.02$, 1.03–1.44)[30]. Five-year overall survival was higher in patients undergoing postoperative radiotherapy at the same facility as their surgery: 52.5% vs 48.4% ($P < 0.001$)[31]. Surgery with adjuvant chemoradiotherapy was associated with improved survival for patients with tongue cancers with ≥2 metastatic lymph nodes and/or pT3–pT4[32].

Discussion

The NCDB has been used widely to study head and neck cancer including OCSCC, mainly to evaluate commonly utilized therapeutic modalities, determine prognostic predictors, identify demographic and socioeconomic factors, and create machine learning algorithms for predicting occult nodal metastasis. The main advantage of the NCDB is that it collects nationwide data from a large sample of patients, which would be difficult to achieve even in well-organized multicenter studies. However, studies based on the NCDB have inherent limitations associated with the database. Firstly, the data are retrospective and subject to omissions and inaccuracies or miscoding of the medical record[9,25]. The NCDB data are captured from Commission on Cancer-accredited hospitals across the United States[19], each with systematic differences in data collection and treatment patterns[22], which ultimately introduces selection bias. Some relevant data are not included in the NCDB and this may create a confounding bias. For instance, tobacco and alcohol use, as well as other comorbidities and performance status, are not recorded[29]. Furthermore, high-risk histological features such as perineural and lymphovascular invasion are not included within the NCDB[17,25,31]. Tumor biology and genetic markers, which are becoming more widely appreciated prognostic factors, are also not recorded in the database[17,26,32]. The specific details of different treatment modalities are not available, such as the levels and laterality of neck dissections[25]. Additionally, radiotherapy modalities do not include the radiation fields or designation of local versus regional treatment[29]. In the same way, the specifics of chemotherapy regimens are not recorded[31,32]. Disease-specific survival or patterns of recurrence including local, regional, or distant failures are not included in the NCDB[32,33]. Furthermore, the DOI is frequently omitted[28] and is not distinguished from the tumor thickness, which is not an interchangeable measurement[25].

It is important to mention that the data recorded in the NCDB have changed over time, and this may explain the differences in findings between the different articles. For example, 2004 was the first year the NCDB began collecting detailed information on radiation treatment. HPV status was only routinely collected for head and neck cancers starting in 2010[34]. However, even after starting to collect this, it is still missing for a lot of patients. Similarly, the Charlson–Deyo comorbidity score was only recorded in the dataset starting in 2003[19], but is not registered in up to one third of cases[22]. Conversely, 2012 was the last year with survival information[32].

The present analysis of OCSCC NCDB studies confirmed the impact of sex, age, ethnicity, and insurance status on survival outcomes[8–12], which is in accordance with the literature[35–38]. Specifically, there are disparities in disease advancement between the sexes and between races, in non-operative treatment between black patients and those of other ethnicities, and in access to higher-performing facilities based on insurance coverage. Discrepancies exist in the literature on patient age, with some studies showing better outcomes for young individuals[39], as shown in the NCDB[8], and others identifying young age as being associated with worse outcomes[40,41]. Importantly, the discrepancies between these studies may be due to differences in the definition of young age, small cohort sizes, and variable disease stages.

This NCDB analysis also showed an improvement in the prognosis of OCSCC between 1998 and 2006, likely due to the increasing use of chemotherapy in advanced-stage disease, improvements in surgical techniques leading to higher rates of negative margins, and more frequently performed elective neck dissections in early-stage disease[14]. Primary surgery alone for early-stage disease, or with adjuvant radiotherapy with or without chemotherapy for advanced-stage disease, has been confirmed to be superior to primary radiotherapy or chemoradiotherapy in multiple studies[20–22,27–32]. These findings are consistent with the 2017 National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines (https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf), which provide level 2A recommendations for primary tumor extirpation with neck dissection. Additionally, primary radiotherapy is associated with a higher mortality, and should be proposed only if surgery is not feasible[20,22]. In advanced-stage cancer, the 2017 NCCN Clinical Practice Guidelines recommend surgery with postoperative adjuvant therapy or multimodality clinical trials for resectable OCSCC. Neck dissection in early stages and more extensive neck dissection in all stages improved the prognosis of OCSCC[24–26]. In early-stage N0 OCSCC, a neck dissection including at least 16 to 24 nodes increased the survival when the DOI was >4 mm in all of the studies. The benefit of neck dissection for a DOI $\leq$ 4 mm is less clear from NCDB analyses[25,27] and other studies in the literature[42,43].

In conclusion, despite its limitations, the NCDB has resulted in a greater understanding of various clinical aspects of OCSCC. This study highlights the major role of surgery and the impact of socioeconomic status on the outcomes of OCSCC. It can be judged that the NCDB is a large and useful database that can aid the clinician in making treatment decisions and evaluating the prognosis. It must be pointed out that the NCDB data give only partial, although very useful, retrospective information regarding demographic, pathological, and treatment details. Therefore, it is important that the results of the various NCDB studies are interpreted critically. Despite these limitations, it is clear that the data can help in clarifying the best practices in the treatment and prognostic evaluation of OCSCC. The database is especially helpful in generating hypotheses and determining effectiveness of treatment options and surgical approaches when prospective data are not available. Also, database data are important for the evaluation of trends in survival and care for cancer patients.

It is clear that definitive evidence on treatment and prognosis must still be derived from well-designed prospective studies and meta-analyses of randomized clinical trials. On the other hand, the NCDB is a very valuable resource for clinicians and researchers involved in the management of OCSCC, offering an incomparable perspective on a very large dataset of patients. Future developments regarding hospital information management, review of data accuracy and completeness, and wider accessibility will help investigators and clinicians to improve the care of patients affected by OCSCC.

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Competing interests

None.

Ethical approval

Not applicable.

Patient consent

Not applicable.

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