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Epidemiological, clinical and oncological outcomes of young patients with laryngeal cancer: a systematic review

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Abstract

Objective To investigate epidemiological, clinical and oncological outcomes of young patients with laryngeal cancer (LC).

Methods PubMed, Scopus and Cochrane Library were searched by three researchers for studies investigating epidemiological, clinical and oncological outcomes of patients with age < 40 years old and LC. The following outcomes were investigated with PRISMA criteria: age; ethnicity; gender; tobacco/alcohol habits; anatomical, pathological, therapeutic and survival features. Authors performed a bias analysis of papers and provided recommendations for future studies.

Results Seventeen papers published between 1982 and 2021 met our inclusion criteria, accounting for 928 patients with age < 40 years (female/male ratio: 2:5). There were on average 54.2 and 45.8% of smokers and drinkers. The tumor location mainly consisted of glottis (70.1%), supraglottis (27.7%) and subglottis (2.2%). Radiation therapy was the main therapeutic strategy used in young adults with LC. The 2-year overall survival ranged from 50 to 100% and depended on tumor stage, treatment, and cohort features. Four studies reported better overall survival in young compared with old adults, while there were no significant differences in three studies. There was an important heterogeneity between studies regarding the inclusion/exclusion criteria, epidemiological, clinical, pathological and treatment.

Conclusion It was suggested that young patients with LC had lower proportion of smokers and drinkers and better overall survival compared with older but both data of the current literature and heterogeneity between studies limit us to draw definitive conclusions.

Keywords Laryngeal · Larynx · Cancer · Squamous cell carcinoma · Otolaryngology · Head neck surgery · Young · Age

Introduction

Laryngeal cancer (LC) is the second most common head and neck cancer, accounting for 211,000 new cases and 126,000 deaths per year worldwide, respectively [1]. Over the past 3 decades, the incidence of LC significantly decreased in males and unchanged or increased in females according to world regions [1, 2]. LC is known to be a malignancy of sixth or seventh decade of life of individuals with tobacco and alcohol consumption histories [2]. Age appears to be an important prognostic factor because elderly patients report stronger therapeutic response and survival outcomes [3]. LC occurs in 2 to 10% of patients younger than 40 years old, who may report less smoking and alcohol consumption compared with older patients [4, 5]. In this group of patients, the development of LC was furthermore suspected to be associated with DNA mutations and genetic abnormalities [6]. Thus, an increasing number of otolaryngologists consider that young patients with LC may present a different oncological disease than elderly patients regarding tumor features, disease history and survival outcomes.

The aim of this systematic review is to investigate epidemiological, clinical and oncological outcomes of young patients with LC.

Giuditta Mannelli and Carlos M. Chiesa-Estomba have equally contributed to the paper and have to be joined as co-senior authors.

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Materials and methods

The criteria for consideration of study inclusion were based on the population, intervention, comparison, outcome, timing and setting (PICOTS) framework [7]. For each included study, two authors (JRL, CMCE and SH) independently reviewed and extracted data regarding the PRISMA checklist for systematic reviews [8].

Eligibility criteria

Prospective and retrospective, controlled, uncontrolled, or randomized studies published between January 1980 and July 2021 were included in this systematic review. Studies were included if they investigated epidemiological, clinical, pathological or oncological characteristics in young adults with LC. In the majority of studies, young patients with LC were commonly defined as patients with age < 40 years old [6]. However, we also included studies where authors used another cut-off. Different types of LC were considered, such as laryngeal squamous cell carcinoma (LSCC), mucoepidermoid carcinoma or sarcoma. The studies had to be published in English, Spanish, or French peer-reviewed journals. Only studies reporting data for more than ten individuals were considered.

Populations, inclusion/exclusion criteria

The authors had to provide inclusion criteria and definition of young patients. Retrospective, prospective, uncontrolled, or controlled studies were eligible if the study cohorts contained at least a group of young adults with LC. Controlled studies comparing young and older patients were considered. The type of study was classified according to the levels of evidence for prognostic studies (I–V) [9].

Outcomes

Three authors (JRL, CC and SH) reviewed the following outcomes: number of patients, definition of young patient, gender ratio, proportion of smoker/drinker in the young patient group, mean or median age, tumor location (glottis, supra- or subglottis, transglottis), histopathology of tumor, tumor stages, treatment and oncological outcomes.

The Tool to Assess Risk of Bias in Cohort Studies developed by the Clarity Group and Evidence Partners was used by two authors (JRL and CC) for the bias/heterogeneity analyses of the included studies [10]. The bias analysis consisted of evaluation of cofactors that may impact the comparison of studies, i.e. epidemiological (comorbidities, tobacco/alcohol use, etc.), clinical, histopathological and therapeutic characteristics of patient age groups.

The following oncological outcomes were evaluated: overall survival (OS), disease-free survival (DFS), disease-specific survival (DSS), recurrence and second malignancy rates.

Intervention and comparison

The following therapeutic approaches were reviewed and analyzed for each study: surgery, radiation, combined treatments, and no treatment. The time of the inclusion of patients was considered in the therapeutic analysis regarding the evolution of some therapeutic approaches over the past four decades (i.e. chemotherapy, radiation).

Timing and setting

There was no criteria for specific stage or timing in the 'disease process' of the study population. Data from population-based registries or clinical hospital studies were considered.

Search strategy

The paper search was conducted on PubMED, Scopus, and Cochrane databases by three independent authors (JRL, SH and CC). The databases were screened for abstracts and titles referring to the description of data of young patients with LC. The authors analyzed full texts of the selected papers. Results of the search strategy were reviewed for relevance and the reference lists of these publications were examined for additional pertinent studies. Any discrepancies in synthesized data were discussed and resolved by the remaining co-authors. The following keywords were included: 'larynx'; 'laryngeal'; 'cancer'; 'young'; 'carcinoma'; 'comparison'; 'old'; 'outcomes'. The three investigators analyzed studies for the outcomes above-mentioned.

Results

A total of 1004 articles were identified and 17 studies published between 1982 and 2021 met our inclusion criteria (Fig. 1) [3–5, 11–24]. Three studies were excluded because authors included patients with laryngeal and non-laryngeal cancers in a same group, without providing specific outcomes for LC [25–27]. All studies were retrospective chart-review (EL: IV). The authors compared different age groups in 10 studies [3–5, 16–22]. A total of 99, 778, 51, and 60 patients with age < 30; < 35; < 40; < 50 years old were included in the present review, respectively. Irrespective to the age groups, the female/male ratio of < 40 years old patients with LC was 234/551. Proportions of smokers and drinkers were available in 9 and 6 studies, respectively (Appendix 1). The proportion of smokers in patients < 40 years old ranged from 38 to 92% ($N = 97/179$; 54.2%) [4, 5, 11, 14, 15, 17, 20, 21, 23]. The proportion of drinkers ranged from 0 to 82% ($N = 44/96$; 45.8%) [5, 15, 17,

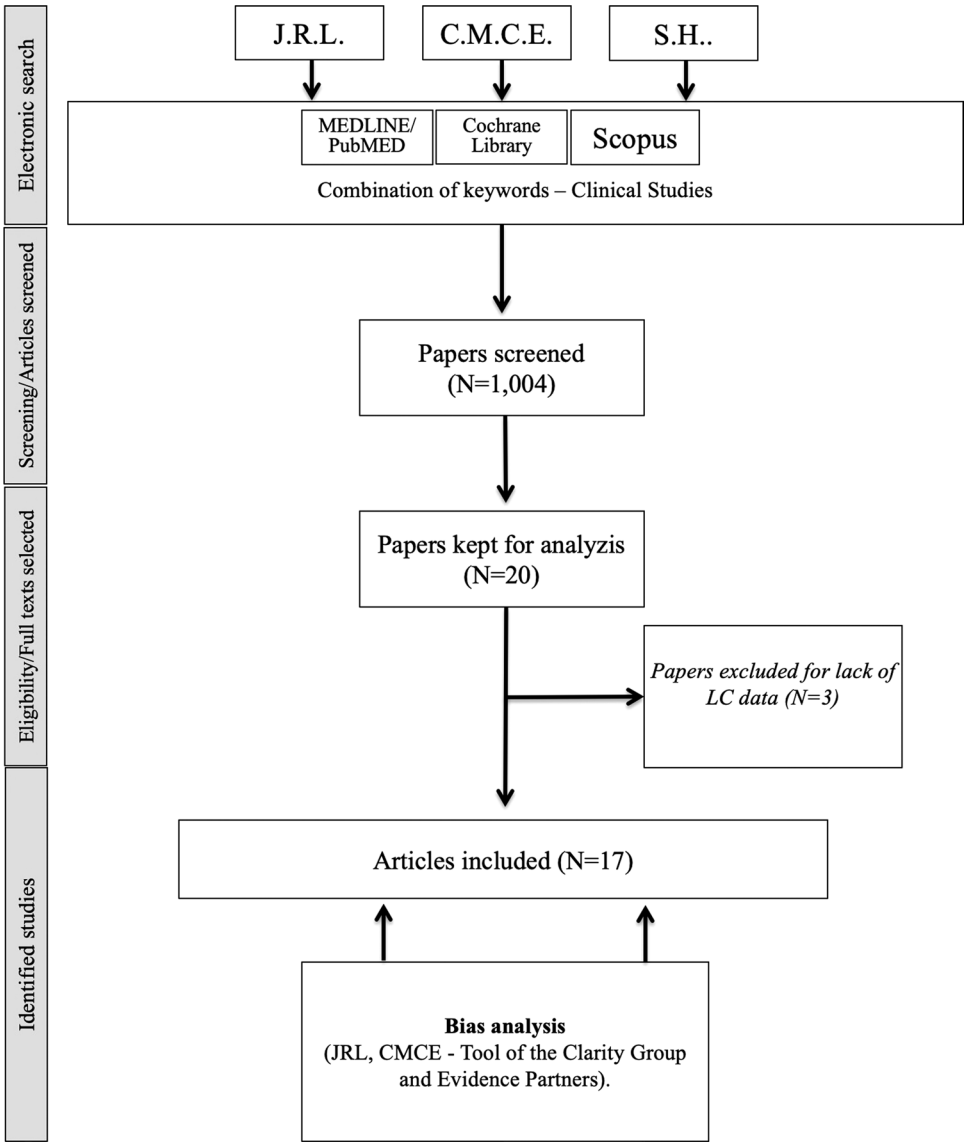

Fig. 1 Chart flow

20, 21, 23] Luna-Ortiz et al. did not find significant differences between age groups about tobacco and alcohol consumptions [20], while Singh et al. observed higher proportions of drinkers and smokers in young compared with old group [17].

Tumor features

Eleven studies only included patients with LSCC [4, 5, 13–18, 21, 23, 24], while others recognized having considered adenoid cystic carcinoma [11], verrucous SCC [19], sarcoma [19], small cell cancer [19], mucoepidermoid [19], and Kaposi sarcoma [19]. Three studies did not specify the LC histology [3, 20, 22]. Location and stage data of studies are summarized in Table 1. LC was located in glottic, supraglottic or subglottic region in 70.1, 27.7 and 2.2% of patients < 40 years old. The majority of LC are discovered in Stage I and III in young adults (Table 1). Among the comparative studies, patients < 40 years old reported similar staging profile than patients > 40 years old in the studies of Luna-Ortiz et al. [20], and Wang et al. [5], while they differed in the study of Nachalon et al. [4] with higher proportions of stage I and II in old patients. In the study of Singh et al. [17] the proportion of supraglottic cancer was significantly higher in old patients compared with young individuals who reported higher proportion of glottic cancers.

Therapeutic strategies

From retrospective chart-reviewed published between 1982 and 2001, the main therapeutic approaches consisted of surgery [11, 13], radiation [12, 14], or both [15, 16]. The therapeutic approaches varied between studies, even if some of them were characterized by a similar proportion of stages I–IV [13–15]. Considering studies conducted from 2009 to

Table 1 Pooled characteristics of tumor features

Tumor features	*N* (%)
Location	
Glottis	297/522 (56.9)
Supraglottis	139/502 (27.7)
Infraglottis	7/317 (2.2)
Transglottis	17/205 (8.3)
Unknown	46/279 (16.5)
Stages	
I	42/106 (39.6)
II	11/106 (10.4)
III	32/106 (30.2)
IV	19/106 (17.9)
Unspecified	2/106 (1.9)

N number

2021, radiation was considered as the main approach for the treatment of LC in young adults in the majority of studies [3, 4, 20, 23, 24]. Only Wang et al. reported a significant higher proportion of surgical treatment in young patients; their cohort being mainly composed of stages I–II [5]. The therapeutic strategies do not seem to have evolved over the study period; while some teams from the same centers [4, 14, 23] seemed to prior some approaches over time.

Oncological outcomes

Considering studies published from 1982 to 2001, data about overall survival were available in fivw studies [11–14, 17]. The 2-year OS of stages I–II or cT1–2 was 100% and decreased to 50 to 66% for stages III–IV [11, 12]. Irrespective to the stage, the 5-year OS ranged from 66 to 100%, with naturally better outcomes in studies with higher proportion of stages I or II [14]. Petrovic et al. reported a 5-year disease-free survival of 84% but they did not report staging information [16]. Benninger et al. assessed the recurrence rate of young adults with LC and at an average follow-up of 50.4 months, they found 62% of recurrences [15]. According to the study of Albright et al. young patients with LSCC had a significant lower risk to develop second malignancy than older patients over time (Appendix 1) [18]. Regarding age group comparisons, Singh et al. did not find significant differences between young and old patients about cTNM, treatment and complication, whereas they reported lower proportions of smokers and drinkers [17]. In this study, the median survival of old patients was significantly lower than those of young individuals [17].

Nine studies were published between 2009 and 2020 [3–5, 19–24]. The 1-year OS ranged from 86 to 100%, and was significantly better in young than old adults with LC [5, 22]. The 5-year survival ranged from 40 to 87% and depended on stages and studies [5, 19, 22–24]. Bezerra et al. reported that young adults had better 5-year OS than old individuals [22], while Wang et al. and Nachalon et al. did not find significant differences across groups [4, 5]. Luna-Ortiz et al. observed mean DFS and OS of 66 and 83 months in young and old patients without differences across groups [20]. Only Rutt et al. compared young patients with each other, and they observed on small cohorts than subjects aged from 15 to 19 years old had better 5-year OS than older 'young' patients [19]. Note that these authors included in the cohort LSCC, verrucous SCC, sarcoma, Kaposi sarcoma, small cell, and mucoepidermoid cancer. In a cohort of young and old patients comparable regarding tumor location, gender ratio and treatment (mainly radiation), Reizenstein et al. reported that OS, disease-specific survival (DSS) and relapse risk were significantly better in young compared with old groups [3].

Bias analysis

Heterogeneity among included articles in inclusion/exclusion criteria, tobacco/alcohol consumption, comorbidities, tumor features, and treatment are described in Table 2. Studies are all retrospective chart-review (EL: IV). Many studies included a low number of young patients compared with old individuals. In four studies, authors based their outcome comparisons between young and old patients or between young patients with LC and young patients with another type of cancer on the data of the literature, without providing a true comparison with a matched patient group [11, 13, 15, 16]. Several histopathologies were considered in six studies [3, 11, 12, 19, 20, 22], whereas authors included pediatric population in the database in two studies [11, 18]. Tobacco and alcohol consumption information are not reported in 8 and 11 studies, respectively (Table 2). Any authors reported information about HPV infection, histories of reflux, occupational carcinogen exposure or neck radiation. Comorbidities of old patients with LC were considered in the oncological analysis in one study [24]. As reported in Appendix 1, at the exception of Reizenstein et al. [3] and Wang et al. [5], authors did not perform uni- or multivariate analyses to evaluate the impact of some factors (i.e. tobacco, alcohol, comorbidities, radiation features) on oncological outcomes. Ethnicity was considered in the analysis of outcomes in two studies [17, 19].

Discussion

The number of publications dedicated to LC in young adults did not increase over the past few decades; the studies covering the period from 1980 to 2021. Yet, according to the increase of incidence of LC in young individuals [2], it remains important for the future decades to better understand the potential disease differences between young and old patients about tumor features and oncological outcomes. In this systematic review, we tried to analyze the current

Table 2 Bias analysis

References	Pathology	Tobacco	Alcohol	Comorbidity	HPV	HNSCCH	RF
Newman [11]	No	Yes	No	No	No	No	No
Webber [12]	Probably no	No	No	No	No	No	No
Mendez [13]	Yes	No	No	No	No	No	No
Shvero [14]	Yes	Yes	No	No	No	No	No
Benninger [15]	Yes	Yes	Yes	No	No	No	No
Petrovic [16]	Yes	No	No	No	No	No	No
Singh [17]	Yes	Probably yes	Probably yes	No	No	Yes	No
Albright [18]	Yes	No	No	No	No	No	No
Reizenstein [3]	No	No	No	No	No	No	No
Rutt [19]	Probably no	No	No	No	No	No	No
Luna-Ortiz [20]	No	Yes	Yes	No	No	No	No
Mafi [21]	Yes	Yes	Yes	No	No	No	No
Bezerra [22]	No	No	No	No	No	No	No
Wang [5]	Yes	Yes	Yes	No	No	No	No
Nachalon [4]	Yes	Yes	No	No	No	No	No
Nachalon [23]	Yes	Yes	Yes	No	No	No	No
Silen [24]	Yes	No	No	Yes	No	No	No

According to the bias tool used, the following points were considered: Pathology: Yes = inclusion of LSCC only; Probably Yes = inclusion of > 95% of LSCC; Probably no = inclusion of 50–95% of LSCC; No = no information about the histopathology or inclusion of < 50% of LSCC. Alcohol/Tobacco/HPV: Yes = data provided for both groups (if > 1 study group); Probably yes = data provided for young adult group; Probably no = data not complete (lack of *N*/% of patients); No = no data. HNSCCH: Yes = authors excluded patients with a history of previous HNSCC; No = Authors did not provide information or included patients with previous history of HNSCC/treatment of HNSCC. RF = consideration of other risk factors: Yes = consideration of all following risk factors: occupational carcinogens; reflux and history of radiation; Probably yes = consideration of 2 of the 3 above-mentioned risk factors; Probably no = consideration of 1 of the 3 above-mentioned risk factors; No = no consideration of above-mentioned risk factors. Comorbidity: Yes = comorbidities of patients were considered in the survival analysis; No = no consideration of comorbidities

HPV human papilloma virus, *HNSCCH* head neck squamous cell carcinoma history, *RF* risk factors

evidence regarding epidemiological, etiological, pathological, and oncological outcomes of young patients with LC. We observed a substantial number of conflicting data, leading to the inability to draw reliable conclusion for many points.

First, it was often argued that patients < 40 years old with LC had a different disease regarding etiological factors than those > 40 years old [6]. Precisely, regarding the findings of the INHANCE consortium [28], 24.1% of patients < 45 years old with HNSCC never smoked, while 13.6% of old patients (> 45 years old) were non-smokers. Similarly, 18.9% of patients < 45 years old with HNSCC did not consume alcohol at the time of the diagnosis, while they are 7.5% in the older group (> 45 years old). In the same study, authors observed 7.5% and 5.4% of non-smokers with LSCC in < 45 years old and > 45 years old patient groups, respectively [28]. In the present review, we assessed the baseline proportions of non-smokers and non-drinkers to 45.8% and 54.2%, respectively, which was higher than the data of the INHANCE group. In practice, these findings tend to support that a substantial proportion of young adults with LC are non-smoker and non-drinker patients and, therefore, may have developed LC regarding additional risk factors, such as laryngopharyngeal reflux, HPV infections, occupational carcinogens, and genetic/ethnicity polymorphisms [6, 29, 30]. However, surprisingly, these important risk factors were not evaluated in many studies included in the present review although they may have a significant impact on oncological outcomes. The lack of information and the pathological heterogeneity between studies limit the draw of clear conclusion about the risk factor differences between young and old patients. The consideration of ethnicity is another example. Indeed, 12% of patients with HNSCC are Black in the U.S., and it has been supported that Whites and Blacks may have significant differences about the genetic pattern, carcinogen susceptibility, and sociodemographic features, all of them being responsible of different clinical presentations of the LC [6, 29, 31]. About gender ratio, we found a female/male ratio of 2/5, which differs from the common 1/7 ratio of patients with LSCC [2]. The equalization of the male to female ratio in the young population may reflect the gender finding observed in tongue cancers of the young adult where genetic pattern and HPV have a key role in the development of cancer in female [6, 32]. Moreover, it is conceivable that the importance of the genetic polymorphism in the development of LC in young adults leads to an inability to really compare future studies conducted in remote world regions. For example, the oncological outcomes of the Chinese study of Wang et al. [5] were substantially different from the studies of Nachalon et al. that were conducted in Israel. [4, 23]

Table 3 Recommendations for future studies

Recommendations
Epidemiological outcomes
1. Authors have to provide the following epidemiological population data for study groups
Ethnicity, gender ratio and age of patients
Histories of tobacco/alcohol consumptions
History of Laryngopharyngeal reflux
Presence of occupational carcinogen exposure
History of familial cancer
History of radiation
2. Authors have to consider pediatric patients (< 18 years old) as a different clinical group than adult patients with LC
Tumor outcomes
1. The tumor histology and grade have to be provided for each patients as well as the cTNM classification used
2. Authors have to specify the tumor location of patients
3. In case of study focusing on laryngeal cancer, only laryngeal tumors have to be included
4. Because the histology and stade of tumor may impact the prognosis, authors have to investigate the oncological outcomes in groups of patients with similar tumor findings (histology, stages, and location)
Oncological outcomes
1. Authors should define the evaluated oncological outcomes (OS, DFS, DSS, recurrence rate, etc.)
2. Authors should consider the higher risk of comorbidities in older groups, which may impact the survival outcomes
3. The data of oncological outcomes should be carefully compared from one study to another considering potential discrepancies
regarding treatments, comorbidities, risk factor exposure, and above-mentioned tumor and epidemiological findings
4. The details about therapeutic strategies are important, including type and time of surgery, radiation and chemotherapy features

DFS disease free-survival, *DSS* disease specific survival, *LC* laryngeal cancer, *OS* overall survival, *yo* years old

Second, our analysis reports that the studies are heterogeneous about tumor location, stages and histology, which limits the study comparison, the realization of pooled analyses and the draw of clear conclusion. Many authors did not focus on squamous cell carcinoma or verrucous carcinoma. The inclusion of pediatric patients in some studies [11, 18], and the consideration of patients with several tumor types (i.e. LSCC, sarcoma, mucoepidermoid, Kaposi sarcoma) may undoubtedly impact the oncological outcomes of studies since pediatric patients with LC are known to report better prognosis than adults [29, 34]. About location, 57% and 28% of tumors were glottic and supraglottic tumors, respectively, while glottic and supraglottic tumors consisted of 76% and 19% of cases in large database studies of young adults [31]. In the study of Singh et al. [17] the proportion of supraglottic cancer was significantly higher in old patient group compared with the group of young individuals who mainly had glottic cancers; this group differences bias the comparison and, therefore, the oncological results of the study. Indeed, supraglottic cancers usually report stronger prognosis than cancer located in the glottis [34].

Third, in the present review, we identified better OS outcomes for young adults in four studies [3, 17, 22, 24], while there were no significant differences between age groups in three papers [4, 5, 20].

In practice, the comparison between studies is again difficult because therapeutic strategies evolved from 1980 to 2021. Moreover, treatments may differ from one center (country) to another; some physicians favoring surgery, while other prefer radiation when the situation allows several choices. The evolution of treatments throughout the past 4 decades and the occurrence of different therapeutic strategies across centers make difficult both the comparison between studies and the establishment of oncological conclusion. At best, our data may suggest that young adults with LC may have better oncological outcomes but that depends on the tumor stage and location and the comorbidities of old patients, this point being not investigated although it has a significant impact on OS of older subjects [35, 36].

Based on the numerous grey areas and study weaknesses that were highlighted in this systematic review, the experts of Laryngeal and Head and Neck Study Groups of Young-Otolaryngologists of the International Federations of Oto-rhino-laryngological Societies propose some recommendations and key points for improving the methodology of future studies (Table 3). These recommendations aim to allow the comparison of future studies using similar and standardized criteria and definitions.

Conclusion

It was suggested that young patients with LC had lower proportion of smokers and drinkers and better overall survival compared with older. However, data of the current literature and heterogeneity between studies regarding inclusion criteria, epidemiological, clinical, pathological and therapeutic outcomes limit us to draw definitive conclusions. Future multicenter large cohort studies considering squamous cell carcinoma are needed to determine if young patients with LC have different clinical disease than old patients.

Appendix 1

See Table 4.

Table 4 Characteristics of patients

References	Design	EL	Cohort	Tumor site (*N* (%))	HP and Stage (*N* (%))	Treatments (*N* (%))	Results	Main findings
Newman [11]	Retrospective	IV	*N* = 33 (< 35 yo)	Glottis: 27 (82)	HP: LSCC & non-LSCC	Surgery or RT: 32 (97)	2y OS: 81%	1. The 2y OS of young patients with LC was 81% with better OS for stages I–II
USA, 1982	Chart-review		F/M: 15/18	Supraglottis: 4 (12)	Stage: NP	Nothing: 1 (3)	Stages I–II: 100%	
			Smokers: 67%	Piriform sinus: 2 (6)			Stages III–IV: 50%	2. In comparison with oral and OSCCs, the OS of young adults with LSCC were better
			Alcoholic: NP					
Webber [12]	Retrospective	IV	*N* = 18 (< 35 yo)	Glottis: 10 (56)	HP: LSCC (17)–Adenoid	RT: 13 (72)	2–10y OS:	1. 3% of LC occured in patients < 35 yo
UK, 1984	Chart-review		F/M: 27/124	Transglottis: 4 (22)	cystic carcinoma (1)	Surgery: 4 (22)	cT1: 100%	2. The OSs were better in cT1, cT2 than cT3 or cT4
			Smokers: NP	Supraglottis: 3 (17)	Stage: cT1: 10 (56)	Combined: 1 (5)	cT2: 100%	
			Alcoholic: NP	Subglottis: 1 (5)	cT2: 6 (17)		cT3: 66%	
					cT3: 3 (17)		cT4: 0%	
					cT4: 1 (5)			
Mendez [13]	Retrospective	IV	*N* = 63 HNSCC	Glottis: 8 (50)	HP: LSCC	Surgery: 9 (56)	5y OS: 87.5%	1. 5y OS of young patients with LSCC was 87.5% and was significantly better than OS of those of patients with pharyngeal/ oral SCC
USA, 1985	Chart-review		*N* = 16 LSCC (< 40 yo)	Supraglottis: 3 (19)	Stage: I: 7 (44)	RT: 3 (19)		
			F/M: 3/13	Transglottic: 5 (31)	II: 1 (6)	Surgery & RT: 4 (25)		
			Smokers: NP		III: 7 (44)			
			Alcoholic: NP		IV: 1 (6)			
Shvero (14)	Retrospective	IV	*N* = 20 (< 40 yo)	Glottis: 13 (65)	HP: LSCC	TL + RT: 6 (30)	5, 10, 15y OS:	1. A high percentage of young adults with LSCC presented with advanced stages
Israel, 1987	Chart-review		Mean age: 30 yo	Glotto-subglottis: 3 (15)	Stage: I: 13 (65)	Radiation: 13 (65)	Stage I: 100–75–75%	
			F/M: 4/16	Supraglottis: 1 (5)	II: 3 (15)		Stage II: 100–100–100%	2. The 5, 10 and 15 OS ranged from 50 to 100% according to tumoral stage
			Smokers: 80%	Transglottis: 3 (15)	III: 4 (20)		Stage III: 66–50–NP%	
			Alcoholic: NP		IV: 0 (0)			

Table 4 (continued)

References	Design	EL	Cohort	Tumor site (*N* (%))	HP and Stage (*N* (%))	Treatments (*N* (%))	Results	Main findings
Benninger [15]	Retrospective	IV	*N* = 13 (< 40 yo)	Glottis: 6 (46)	HP: LSCC -No stage: 2 (16)	RT + Surgery: 5 (39)	Recurrence (%): 62%	1. 62% of patients with LSCC had local/ distant recurrence (average follow-up: 50.4 months)
USA, 1988	Chart-review		Mean age: 36 yo F/M: 3/10	Subglottis: 7 (54)	Stage: I: 3 (23) II: 1 (8)	Surgery + RT: 3 (23) RT: 4 (31)		
			Smokers: 92% Alcoholic: 92%		III: 4 (31) IV: 3 (23)	Surgery: 1 (8)		2. Young adults with LSCC reported poorer OS than usual older patients
Petrovic [16]	Retrospective	IV	Gr1: < 30 (*N* = 4)	Glottis: 32 (52)	HP: LSCC	P/TL: 22 (36)	5y DFS: 84%	1. The 5y DFS of patients < 40 yo with LSCC was 84% and was not significantly lower than patients > 40 yo treated in the same center and the same period (OS: 68%)
Serbia, 1996	Chart-review		Gr2: 31–40 (*N* = 57) F/M: NP Smoker/alcohol: NP	Supraglottis: 29 (48)	Stage: NP	Surgery/RT: 28 (46)		
Singh [17]	Retrospective	IV	Gr1: < 40 (*N* = 20)	Glottis: Gr1–2–3:	HP: LSCC	NP	Recurrences (13–25 m):	1. There were no differences in TNM stage, treatment, or treatment complications across age groups. Young patients had lower % of Smoker, drinker, and high % of HIV infection
USA, 2000	Chart-review		Gr2: 40–79 (*N* = 174) Gr3: > 79 (*N* = 15)	8 (40)–80 (46)–NP Supraglottis:	Tumor stage median: Gr1: III		Gr1,2,3: 35–26–60% Median survival (m):	
			F/M: 7/13	Gr3: 9 (60)	Gr2:III		Gr1,2,3: 45–79–13 months	
			Smoker: 50% Alcoholic: 57%		Gr3: II		HIV proportion: Gr1, 2, 3: 50–3.4–0%	2. The median survival of older patients was significantly lower than those of young and middle age patients
Albright [18]	Retrospective	IV	Gr1: 364 (< 40 yo)	NP	HP: LSCC	NP	Second malignant tumor %	1. Young patients with LSCC had a lower risk to development second malignacy compared with older patients
USA, 2001	Chart-review		Gr2: 22,786 (> 40 yo) F/M: 117/247		Stage: NP		Gr1: 8.2% Gr2: 21.4%	

Table 4 (continued)

References	Design	EL	Cohort	Tumor site (*N* (%))	HP and Stage (*N* (%))	Treatments (*N* (%))	Results	Main findings
			Smokers: NP				5, 10, 15y Relative risk of SMT	2. The most prevalent site of second cancer in young patients are lung (23.5%) and oral cavity (11.8%)
			Alcoholic: NP				Gr1: 3, 6.8, 10.7% Gr2: 14.2, 28.1, 39.4%	
Reizenstein [3]	Retrospective	IV	Gr1: < 50 (*N* = 60)	Glottis: Gr1–4: 47 (78)–	HP: NP	Total laryngectomy:	OS: Gr1 > Gr2,3,4	1. Location, gender ratio and recurrence site were comparable between groups
Sweden, 2009	Chart-review		Gr2: 50–69 (*N* = 473)	352 (75)–238(80)–88 (78)	Stage: NP	Gr1–2: 5 (8)–65 (14)	DSS: Gr1 > Gr2,3,4	
			Gr3: 70–79 (*N* = 298)	Supraglottis: Gr1–4: 10 (17)–		Gr3–4: 19 (6)–4 (3)	Relapse risk: Gr1 > Gr2,3,4	2. OS and DSS were better in young adults Relapse risk was lower in elderly (12%) Compared with youngest (23%)
			Gr4: > 79 (*N* = 114)	107 (23)–49 (17)–20 (18)		Curative RT:		
			F/M (Gr1): 9/51	Subglottis: Gr1–4		Gr1–2: 46 (77)–355 (75)		
			Smoker: NP	3 (5)–10 (2)–9 (3)–5 (4)		Gr3–4: 232 (78)–80 (70)		3. Age, higher cT and *N*+ were the most Important negative prognostic parameters
			Alcoholic: NP					
Rutt [19]	Retrospective	IV	Gr1: < 15 (*N* = 5)	Glottis: 67 (68)	HP: LSCC, verrucous SCC,	NP	5y relative survival:	1. Young patients aged from 15 to 19 yo may present stronger 5y survival than older patients
USA, 2010	Chart-review		Gr2: 15–19 (*N* = 6)	Supraglottis: 18 (18)	Sarcoma, Kaposi, Small		Gr2,3,4: 60–88–87%	
			Gr3: 20–24 (*N* = 26)	Subglottis: 3 (3)	cell, mucoepidermoid LC		Gr3 & 4 > Gr2	
			Gr4: 25–29 (*N* = 62)	Cartilage: 2 (2)	Stage: NP			
			F/M: 52/47	Unspecified: 9 (9)				
			Smoker/alcohol: NP					
Luna-Ortiz [20]	Retrospective	IV	Gr1: < 40 (*N* = 15)	Glottis:	HP: NP	Surgery:	Recurrence (%): 47%	1. There were no significant differences in tobacco/alcohol consumptions and demographic data between age groups
Mexico, 2011	Chart-review		Gr2: > 40 (*N* = 33)	Gr1–2: 10 (67)–23 (70)	Stage: I (Gr1–2):	Gr1–2: 5 (33)–25 (76)	Mean DFS (Gr1): 66 m	
			F/M: 6/9	Supraglottis:	4 (27)–8 (24)	RT:	Gr1 = Gr2	
			Mean age: 34 yo	Gr1–2: 4 (27)–10 (30)	II (Gr1–2): 0 (0)–0 (0)	Gr1–2: 9 (60)–7 (21)	Mean OS (Gr1): 83 m	2. Mean DFS and OS were comparable between age groups
			Smoker (Gr1–2): 73–85%	Subglottis:	III (Gr1–2): 6 (40)–15 (45)	CT:	Gr1 = Gr2	
			Alcoholic (Gr1–2): 60–82%	Gr1: 1 (7)	IV (Gr1–2): 5 (33)–10 (30)	Gr1: 1 (7)		

Table 4 (continued)

References	Design	EL	Cohort	Tumor site (*N* (%))	HP and Stage (*N* (%))	Treatments (*N* (%))	Results	Main findings
Mafi [21]	Cross-sectionnal	IV	*N* = 262 HNSCC	NP	HP: LSCC	NP	Location (patients < 40 yo):	1. Among HNSCC, age was significantly associated with laryngeal location
Iran, 2012	Retrospective		*N* = 210 LSCC		Stage: NP		1. Larynx (40%)	
			Gr1: < 40 (*N* = 6)				2. Tongue (40%)	2. In young patients, the two most common tumor site were larynx (40%) and tongue (40%)
			Gr2: > 40 (*N* = 204)				Location (patients > 40 yo):	
			F/M (Gr1): 2/4				1. Larynx (83%)	
			Smoker (Gr1–2): 67–81%				2. Tongue (11.3%)	
			Alcoholic (Gr1–2): 0–22%					
Bezerra [22]	Retrospective	IV	Gr1: < 40 (*N* = 51)	Glottis: 706 (31)	HP: NP	NP	1y OS (%): Gr1 > Gr3	1. Young adults reported better observed OS than older patients
Spain, 2012	Chart-review		Gr2: 40–64 (*N* = 1404)	Supraglottis: 829 (37)	Stage: NP		Gr1–3: 86–89–82%	
			Gr3: > 65 (*N* = 826)	Subglottis: 21 (1)			3y OS (%): Gr1 > Gr3	
			F/M: 51/2230	Unknown: 709 (31)			Gr1–3: 75–71–63%	
			Smokers: NP				5y OS (%): Gr1 > Gr3	
			Alcoholic: NP				Gr1–3: 75–64–55%	
Wang [5]	Retrospective	IV	Gr1: 34 (< 40 yo)	Glottis: 22 (65)–278 (74)	HP: LSCC	Surgery: 34 (100)	1–3–5y OS (Gr1):	1. Young patient group reported a significant lower proportion of non-smokers than older
China, 2015	Chart-review		Gr2: 374 (> 40)	Supraglottis: 11 (32) –	Stage I–II (Gr1–2):	Post-RT: 15 (44)	100–79–68%	
			F/M: 0/34	82 (22)	21 (62)–247 (66)		1–3–5y OS (Gr2):	2. 1, 3, and 5y OS were similar between Gr
			Smokers (Gr1–2): 59–70%	Infraglottis: 1 (3)–14 (4)	Stage III–IV (Gr1–2):		100–76–66%	3. Age, alcohol & tobacco status did not appear to be prognostic factor of 5y OS
			Alcoholic (Gr1–2): 59–30%		13 (38)–127 (34)			
Nachalon (4)	Retrospective	IV	Gr1: < 40 (*N* = 13)	Glottis:	HP: LSCC	Surgery:	Recurrence (%):	1. The proportion of smokers/alcoholic was lower in young than old patients
Israel, 2017	Chart-review		Gr2: > 40 (*N* = 147)	Gr1: 7 (54)	Stage:	Gr1–2: 3 (23)–38 (26)	Gr1,2: 31–18%; Gr1 = 2	

Table 4 (continued)

References	Design	EL	Cohort	Tumor site (*N* (%))	HP and Stage (*N* (%))	Treatments (*N* (%))	Results	Main findings
			F/M: NP	Gr2: 89 (61)	I (Gr1–2): 3 (23)–62 (42)	RT:	5y OS:	2. There were no significant differences in recurrence/OS between age groups
			Smokers (Gr1–2): 38–71%	Supraglottis:	II (Gr1–2): 2 (15)–32 (22)	Gr1–2: 10 (76)–104 (71)	Gr1,2: 69–90%; Gr1 = 2	
			Alcoholic: NP	Gr1: 6 (46)	III (Gr1–2): 3 (23)–20 (14)	CT:		3. Young adults had higher rates of late- stage disease at presentation
				Gr2: 58 (39)	IV (Gr1–2): 5 (38)–33 (22)	Gr1–2: 6 (46)–54 (37)		
Nachalon [23]	Retrospective	IV	*N* = 29 (< 40 yo)	Glottis: 20 (69)	HP: LSCC	Surgery: 11 (38)	Recurrence (%): 12 (41%)	1. Features and behavior of LSCC in young patients may be similar to older adults
Israel, 2017	Chart-review		Mean age: 35 yo	Supraglottis: 6 (21)	Stage: I: 12 (41)	RT: 21 (72)	2y OS: 86%	
			F/M: 4/25	Unknown: 3 (10)	II: 4 (14)	CT: 5 (17)	5y OS: 79%	2. Higher rates of 2y TL-free survival were noted in patients treated after the organ preservation era without OS differences
			Smokers: 59%		III: 8 (28)		31y OS: 15 (51%)	
			Alcoholic: 3.4%		IV: 5 (17)			
Silen [24]	Retrospective	IV	*N* = 151 (< 40 yo)	Glottis: 67 (44)	HP: LSCC	Surgery: 22 (17)	5, 10y OS: 84–75%	1. Glottic SCC reported better 5- and 10 yo OS and DSS in young adults compared with supraglottic SCC
Sweden, 2019	Chart-review		Mean age: 35 yo	Supraglottis: 47 (31)	Stage: 0: 9 (6)	RT: 50 (39)	Stages I–II: 93–88%	
			F/M: 27/124	Subglottis: 1 (1)	I–II: 91 (60)	CRT: 6 (5)	Stages III–IV: 55–40%	
			Smokers: NP	Transglottis: 2 (1)	III–IV: 34 (23)	Surgery + CRT: 52 (40)	5, 10y DSS: 88–83%	2. Second primary tumor appeared in 26% of patients with a median delay of 28 years
			Alcoholic: NP	Unknown: 34 (23)	Unknown: 17 (11)		Stages I–II: 96–62%	
							Stages III–IV: 93–55%	3. LSCC recurred in 28% of cases

Data presented in this table were reviewed by three authors. Tumor and treatment information were specified for young and old groups when they are available

F/M female/male, *EL* evidence level, *HNSCC* head neck squamous cell carcinoma, *HP* histopathology, *LC* laryngeal cancer, *LSCC* laryngeal squamous cell carcinoma, *N* number, *NP* not provided, *OSCC* oral squamous cell carcinoma, *RT* radiation, *P/TL* total pharyngo/laryngectomy, *y* year(s)

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