HEAND AND NECK

Patients' survival after free flap reconstructive surgery of head and neck squamous cell carcinoma: a retrospective multicentre study

Sopravvivenza dopo chirurgia ricostruttiva con lembi liberi nel carcinoma spinocellulare del distretto cervico facciale: studio retrospettivo multicentrico

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SUMMARY

Head and neck squamous cell carcinoma of the (HNSCC) represents approximately 5% of malignant tumours in Italy. HNSCC are commonly treated with surgery or radiotherapy, or a combination of such therapies. The objectives of treatment are maximum cure rate balanced with organ preservation, restoration of form and function, reduction of morbidities and improvement or maintenance of the patient's quality of life. Immediate reconstructive surgery: local, regional or free flaps are now widely advised in the treatment of these patients. Microsurgical transfer requires expertise, is time and resource consuming, and as a whole requires substantial costs. These considerations introduce some concerns about the wide or indiscriminate use of free flap reconstructive surgery. When considering cost-benefit outcomes of such treatment, the main objective is undoubtedly, survival. This data is underreported in the current literature, whereas functional outcomes of free flaps have been largely diffused and accepted. This study collects data from 1178 patients treated with free flap reconstructive surgery following ablation of HNSCC in a group of Italian tertiary hospitals, all members of the Head & Neck Group affiliated with the Italian Society of Microsurgery. According to many authors, free flap surgery for HNSCC seems to be a beneficial option for treatment even in terms of survival.

KEY WORDS: Head and neck tumours • Free flap • Survival

RIASSUNTO

I tumori spinocellulari del distretto Cervico Facciale rappresentano circa il 5% dei tumori maligni in Italia. Essi sono comunemente trattati con chirurgia o radioterapia, o entrambi le terapie. La ricostruzione rappresenta un momento fondamentale della terapia nel rispetto della qualità di vita di questi pazienti. La microchirurgia ricostruttiva rappresenta la tecnica che offre i migliori risultati funzionali ma è oggetto di discussione in un rapporto costo-benefici. In questo lavoro sono raccolti ed analizzati i dati di 1178 pazienti provenienti dai membri del gruppo testa e collo, affiliato alla società Italiana di Microchirurgia, e i cui dati sono rapportati primariamente alla sopravvivenza.

PAROLE CHIAVE: *Tumori cervico-facciali • Lembi liberi • Sopravvivenza*

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Introduction

Head and neck squamous cell carcinoma (HNSCC) represents approximately 5% of malignant tumours in Italy. Well-recognised or suspected aetiological agents for most HNSCC occurrences are alcohol and tobacco consumption, oral lichen, misfit of prosthetic devices and comorbidities. Recently, human papilloma viruses have been causally associated with some oropharyngeal cancers [1]. According to the site of origin, HNSCC are commonly treated with surgery or radiotherapy, either alone or in combination; medical therapy (i.e. cytotoxic drugs, monoclonal antibodies) is often associated. The objectives of

such treatment are maximum cure rate balanced with organ preservation, restoration of form and function, reduction of morbidities and improvement or maintenance of the patient's quality of life.

Immediate reconstructive surgery is now widely advised in these patients. Local or regional flaps have a definite role in limited lesions and specific situations. Simple or composite free flaps allow *anatomical* repair of almost all defects after HNSCC ablation, whereas *functional* recovery is not always a guaranteed consequence of reconstruction. Microsurgical transfer requires expertise, is time and resource consuming, and as a whole implies significant costs [2]. These points introduce some concerns about wide or indiscriminate use of this technique. Mücke et al. [3] remark that some authors advocate that free flap reconstruction should be reserved to selected patients, namely those who are believed to have a better prognosis. Patients affected by local advanced-stage tumours have worse prognosis, but quite often they are those requiring an adequate reconstruction following extensive ablation [4]: in terms of cost-benefit analysis, these patients should receive fewer benefits from such complex surgery. However, when considering cost-benefit outcomes of such treatment, the main objective is, undoubtedly, survival. This data is underreported in the current literature, whereas functional outcomes of free flaps have been largely diffused and accepted [5 11].

The aim of this study is analysis of survival data in patients treated with free flaps following ablation of HNSCC in a group of Italian tertiary hospitals, all of which are members of the Head & Neck Group affiliated with the Italian Society of Microsurgery.

Materials and methods

Patients

Patients were recruited from centres indicated in Table I. Each participating centre was responsible for reviewing charts and collecting their own data in a database specifically constructed for this study. The study period spanned from the date in which free flap surgery was introduced in each hospital up to December, 31, 2008.

Only patients with demonstrated HNSCC were considered eligible for this case study, and those affected by other malignancies (i.e. sarcomas, malignant melanoma, salivary tumours, etc.) were deliberately excluded, in order to reduce the variability of prognostic factors. A multicentre study was proposed to acquire a larger quantity of cases available for analysis and a joint, elementary database was formed.

Subjects were included irrespective of being a candidate to free flap surgery as part of primary treatment or salvage surgery (Table II, including basic demographic data). All patients who underwent neoadjuvant chemotherapy were assigned to the previously untreated group;

Table I. Participating Centres.

Name of Centre
Istituto Nazionale Tumori, Milan
Clinica ORL, Università di Pavia, Pavia
Istituto Europeo di Oncologia, Milan
Clinica ORL, Università di Brescia
Clinica ORL, Università di Bologna
Ospedale Martini, Torino
Ospedale San Giuseppe, Milan
Ospedale Forlanini, Roma
Chirurgia Maxillo-Facciale, Università di Milano-Bicocca
Clinica ORL, Università di Ferrara

Table II. Patient characteristics (N = 1178).

Characteristics	Value (%)
Age, years	
Median	58
Range	17-85
Gender	
Male	851 (72.2)
Female	327 (27.8)
Previous treatment	
NO	791 (66.3)
Recurrence	397 (33.7)
Margins	
Clear	958 (81.3)
Involved	220 (18.7)
Site	
Oral cavity	842 (71.5)
Larynx-hypopharynx	188 (16.0)
Pharynx	83 (7.0)
Cranio-maxillo-facial	65 (5.5)
pT	
pT0/pTx	33 (2.8)
pT1	51 (4.3)
pT2	349 (29.6)
pT3	165 (14.0)
pT4	580 (49.2)
pN	
N0	559 (47.5)
N+	557 (47.3)
Nx	62 (5.2)
Adjuvant therapy	
NO	557 (47.3)
RT	434 (36.8)
CT+RT	133 (11.3)
CT	33 (2.8)
Na	21 (1.8)

for any other preoperative treatment patients had received despite the circumstance, they were attributed to the salvage surgery group.
All reconstructions were performed at the same ablative episode and, whenever possible, a two-team approach was used.
Due to the number of subsites of tumour origin, some data dispersion would have been expected, and therefore only major categories were considered and subjects were grouped according the main affected site (Table II). Similar belief about pT stratification (Table II) led us to not consider it in survival analysis.
All subjects were treated with curative intent with the aim of complete surgical ablation. Clearance of resection margins (involved or close to less than 5 mm were considered adverse event), pathological nodal status (any pN+ was defined as an adverse event) and adjuvant treatment, all recognised important prognostic factors, were also recorded and analysed.
Flap type and success rate were also investigated, but data were not reported as they were considered beyond the scope of this study.
The survival duration period was defined as the interval from surgery (see above) and the day of death from cancer or the end of follow-up (disease-specific survival, DSS).

Data analysis

Data from each participating hospital were compiled in a single database by appending them. Statistical analysis was performed with the software WinStat® for Excel (R. Fitch Software, Staufen, Germany).
The analysis was conducted according to the "intention to treat" method. Subsequently, the "worst-case scenario" (i.e. adverse event) was assumed when one of the following conditions occurred: patient lost to follow up within 2 years from surgery, in the case of "not evident disease" (NED) at the last update; patient still under control and in the case of "not evident disease" (NED) at the last update, but whose follow up period was shorter than 2 years; perioperative (within 30 days from surgery) deaths were included in the analysis and were, of course, labelled as an adverse event.
A 5-year DSS was used as the dependent variable and calculated according to the Kaplan-Meier method.
Possible predictor variables associated with DSS were: gender, previous treatment, site, clear margins, pathological nodal status and adjuvant therapy. Significant variation among groups was investigated by the log-rank test and qualitative variables were evaluated using a non-parametric test (Chi square test). DSS, instead of overall survival, was chosen as it better depicts the natural history of HNSCC.
Multiple Cox proportional hazards regression models were conducted to explore the relationship between survival and variables believed to affect outcome.

Results

A total of 1178 patients met the criteria for eligibility; most had advanced loco-regional disease (Table II). Clear margins were obtained in 958 cases (81.3%). The ability to achieve complete resection did not strictly correlate to previous treatment ($p = 0.06$). Monolateral or bilateral neck dissection were part of the treatment in 1116 (94.7%) cases. Pathological examination revealed that 559 (50.1%) patients had some degree of nodal involvement. A total of 551 (46.8%) patients developed recurrence after free flap surgery: of these, 22 (4.0%) were salvaged. Perioperative deaths occurred in 19 cases (1.6%). The mean and median DSS were 44.4 and 30.6 months, respectively. The probability of 5-year DSS is shown in Figure 1.
The possible influence of known prognostic factors was investigated. The probability of 5-year DSS according to sex, primary tumour region, margins of resection and adjuvant therapy are shown in Figure 2 (A, B, C, D) , to previous treatment in Figure 3 and to pathological nodal status in Figure 4.
Patients who were operated due to recurrence did worse than those of first observation, (including 48 patients who received neoadjuvant chemotherapy): their chances were 43.1% and 54.1%, respectively ($p < 0.001$). Considering the completeness of resection, a higher rate was obtained in the primary treatment than the relapsing group, even though the difference did not reach statistical significance ($p = 0.060739$). On the other hand, the primary treatment group had more pN positive cases than the relapsing group ($p = 0.03285$).
Involvement of regional nodes also negatively affected the outcome (40.5% vs. 62.9%, $p < 0.001$). Sex, age, margins of resection and adjuvant therapy were not associated with survival.

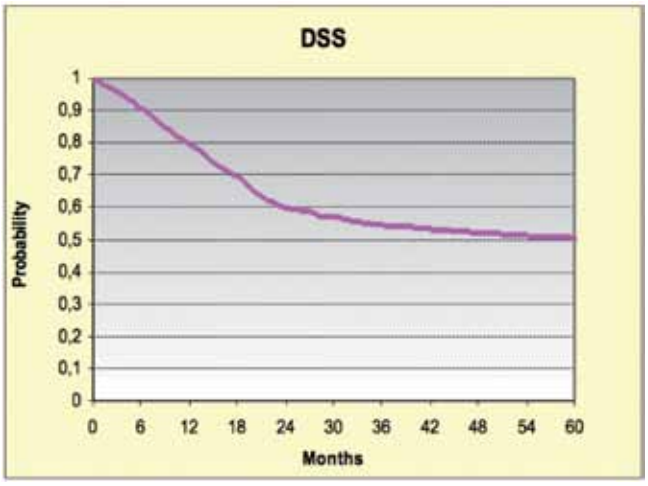

Fig. 1. Disease-specific survival calculated according to the Kaplan-Meier method.

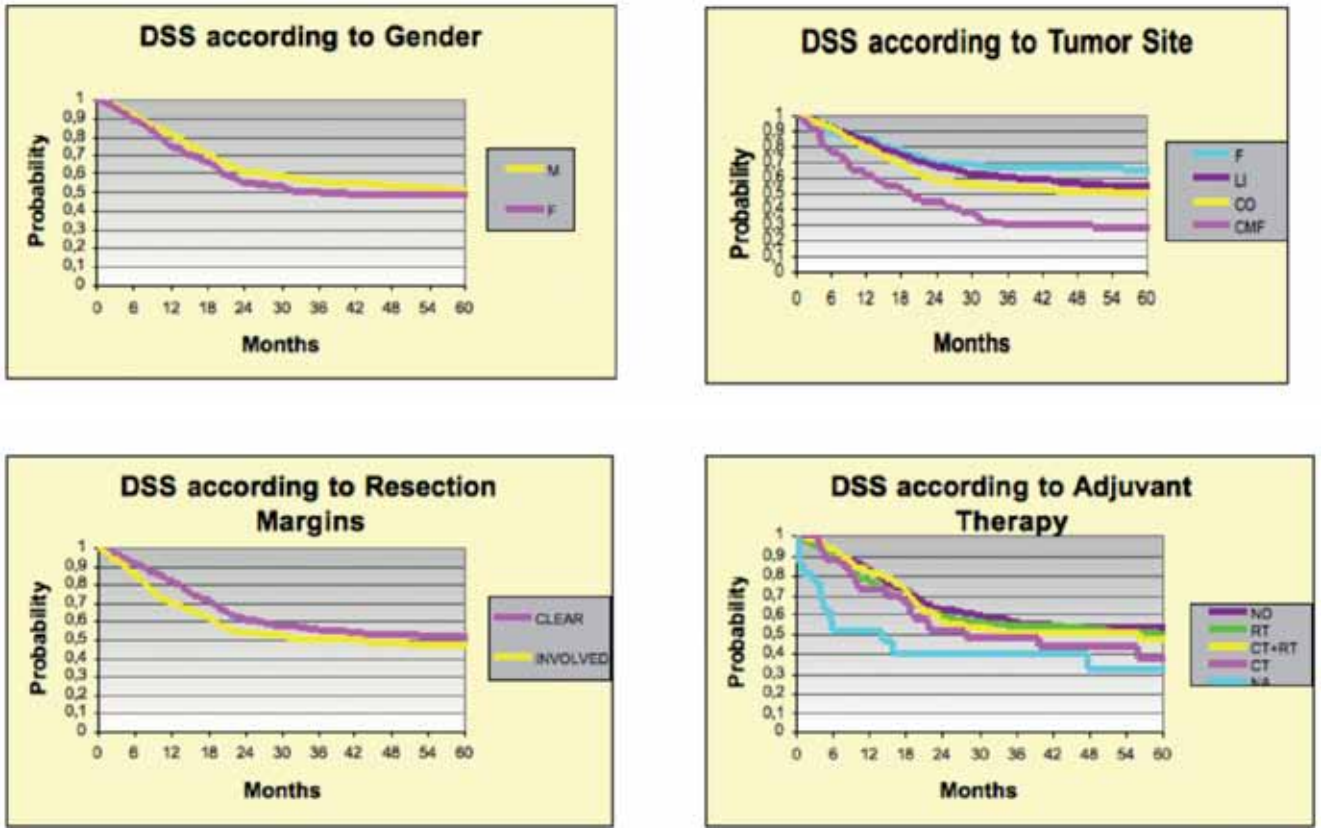

Fig. 2. The probability of 5-year DSS according to sex, primary tumour region, margins of resection and adjuvant therapy calculated according to the Kaplan-Meier method.

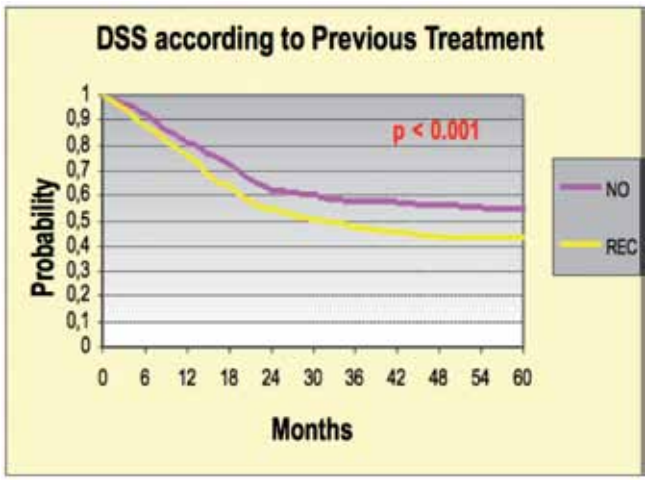

Fig. 3. The probability of 5-year DSS according to previous treatment calculated according to the Kaplan-Meier method.

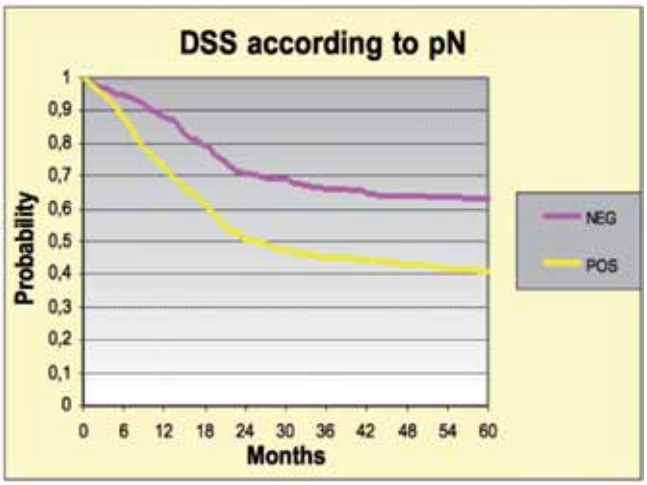

Fig. 4. The probability of 5-year DSS according to pN calculated according to the Kaplan-Meier method.

A Cox proportional hazard regression model analysis was conducted, controlling for sex, age, primary tumour region, previous treatment, margins of resection, pathological nodal status and adjuvant therapy. Female gender, previous treatment and pathologically positive nodes were associated with worse prognosis. The hazard ratios were 1.2, 1.6 and 1.9, respectively (Table III).

Discussion

Free flaps allow a wide range of quality and shape of tissues that can be used for complex anatomical and functional reconstructions. Disadvantages include expertise and higher costs of execution. This has to be taken into account when allocating resources, both at central (i.e.

Table III. Cox regression analysis.

Characteristics	P value	HR
Gender F	0.4	1.2
Recurrence	< 0.001	1.6
pN+	< 0.001	1.9
Age	0.75	
Involved margins	0.19	
Adjuvant therapy	0.4	

health authority) and local (i.e. hospital or department) levels [2], particularly considering the limited economic resources available. This might lead to selection of patients who are suitable candidates for free flap reconstruction: while excellent functional results with free flap surgery for HNSCC have been widely demonstrated [5-11], limited data are available concerning survival of these patients. This study was designed to depict an actual, panoramic view of free flap surgery for HNSCC. Intentionally, only a few, well defined prognostic factors were taken into account.

Inclusion criterion was limited to SCC because this accounts for about 90% of head and neck malignancies: the large prevalence of SCC would allow building up a large series, whose analysis is more likely to produce significant results. Indeed, this paper presents the largest series to date on this subject.

A multicentre study was proposed to acquire a larger quantity of cases available for analysis. Possible biases might have derived from different treatment policies, or expertise among the participating hospital. We tried to reduce these by involving centres that share basic principles of treatment and by building a joint, elementary database. No patients were excluded from the survival analysis, and those lost to follow-up were considered under the most pessimistic hypothesis.

Five-year DSS of the whole series was 50.4%. Sites of tumour origin were grouped in four arbitrary regions: oral cavity (OC), pharynx (PH), larynx-hypopharynx (LH) and cranio-maxillo-facial (CMF), considering that each region poses particular tasks in terms of approach, resection and reconstruction. Survival was worse (27.2%) in patients suffering from CMF tumours than other areas (PH = 65.5%, LH = 54.5%, OC = 49.7).

Gender and age did not correlate with survival. The medical literature alternatively affirms or denies such a correlation, and as such a conclusive statement seems unlikely.

Patients operated on because of relapsing tumour had lower 5-year DSS than those of the first observation (43.1% and 54.1%, respectively, $p < 0.001$). Differences between these groups with regards to completeness of resection and pathological N status confirms that local control remains the main goal: it also seems reasonable to suppose relapsing cancers have more aggressive local behaviour that, in turn, carries worse prognosis.

The incomplete resection rate was 18.7%, which is quite disappointing since it does not fulfill the hypothesis that availability of outstanding flaps should allow wider and safer resections. The ability of achieving complete resection slightly correlated with previous treatment ($p = 0.060739$). Indeed, one could theorise that resection of previously untreated cancer would be easier as the surgeon operates in a relatively unaltered field and chances of microscopically free margins would be greater than in a disordered anatomical set. However, 5-year DSS was similar between the groups with or without clear margins (51.0% vs. 47.3%, $p = 0.14895$). It is widely accepted that adjuvant therapy increases chances of survival. Patients with involved margins were *ipso facto* all candidates for some adjuvant therapy, when feasible (167/220, 75.9%), whereas patients with clear margins underwent adjuvant therapy less frequently (433/958, 45.2%). We suppose adjuvant radiotherapy improved survival in both groups by the same rate, but the impact was reasonably more evident for the involved margins group, as a higher proportion of patients underwent this treatment; this is a possible explanation of the minimal, not statistically significant difference between the two DSS curves.

Pathological nodal status is a powerful, largely independent prognostic factor. This study confirms this data: pN-negative patients did significantly better than pN-positive ones (62.8% vs. 40.6%; $p < 0.001$). Nodal metastases are thought to be an expression of intrinsic tumour offensiveness, whose treatment requires an aggressive approach (i.e. combined therapy): data from the present series lead us to suppose adjuvant therapy was only partially able to fill the survival gap between pN-negative and pN-positive patients. Survival data, to our knowledge, can only be compared to the 32% reported by Podrecca et al [11]. In that series there was a significant proportion (27.2%) of advanced tumours affecting the cranio-maxillo-facial (CMF) region, commonly believed to carry a poor prognosis, whereas in the present series tumours from CMF region accounted only for 5.5%: thus, the prognostic negative impact on the whole series is weakened. This seems a sustainable, even partial, explication of the difference between the two series.

Despite the lack of studies fully comparable to the present one, there is some published data concerning survival after free flaps for HNSCC. Lidman and Niklasson [12] reported the results of free flap surgery in primary intraoral SCC group of 79 patients, most in stage I (42%); they found a 5-year, tumour related, survival of 58%. Hanasono et al. [13] reviewed a group of previously untreated, T3-T4, oral SCC forming two subsets: patients operated without free flaps and with reconstruction (of whom, 66% were free flaps). The first group included a lower rate of advanced tumours than the reconstructed group. They reported a 5-year overall survival (OS) of 37% in the latter subset and no difference with the non-reconstructed patients (42% OS): incompleteness of resection decreased

from 18% to 7%, but no positive impact was demonstrated on survival or local relapse.

Kostrzewa et al. [14], in a series of recurrent oral and oropharyngeal SCC including a large proportion of stage III-IV tumours, reported a 5-year disease-specific survival of 43.7%. Staging, margins and previous treatment were not associated with survival. On the other hand, pathologically-affected nodes, short interval between primary treatment and salvage surgery (or between salvage surgery and relapse) were important negative prognostic factors.

Finally, Mücke et al. [3] have recently described their experience on 274 oral cavity SCC patients operated on with free flaps, comparing them with 499 patients from the same institution, but treated without reconstruction or local/regional flaps. The overall incomplete resection rate was 17.5% (specific data for each group were not reported). Patients with involved margins or relapse within six months from treatment were excluded from the survival analysis. Relapse rate was similar within the two groups. Five-year overall survival was 66.2% in the free flap subset and 58.8% in the no free flap subset. Clinical T and N stage, grading, age and free flap were identified as prognostic factors in both univariate and multivariate analysis. The matched-pair analysis showed better survival in the free flap group, but limited to T3-4 stage patients (no difference for T1-2).

Conclusions

This study investigates the *quoad vitam* outcome of a large (the largest, to our knowledge) series of HNSCC patients treated with free flaps. Efforts were made to depict the actual setting that the Head & Neck surgeon faces in his/her daily activity (limited exclusion criteria, "worst-case scenario" survival analysis). Survival rates are comparable, if not somewhat better, to those reported by different authors worldwide. Free flap surgery seems to have extended the concept of resectability, even if incompleteness of resection remains a pitfall (whose impact on survival appears to be uncertain). Salvage surgery has poorer results than primary surgery. Nodal involvement significantly decreases chances of survival. According to many authors, free flap surgery for HNSCC seems to be a beneficial option of treatment even in terms of survival. Further research is planned to refine the survival analysis. This, in turn, would help both to optimize surgical indications and to compare results to those obtainable from other therapies (i.e. chemoradiation for oro-pharyngeal SCC).

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