**Introduction**

Oral cancer is the 8th most common neoplasm worldwide with 300,000 cases annually. It presents extensive variability in terms of incidence between different regions and is highest in southeast Asia. In Italy, about 4/100,000 new cases per year are documented and it is most common in areas where voluptuary habits such alcohol consumption and tobacco smoking are more diffuse.
Surgery is considered the gold standard to achieve tumour control, but the diagnosis is usually late when the disease has already reached an advanced stage, for this reason, in the majority of cases, neoplasms dimensions, combined with the necessity of clear margins at least 1 cm around the tumour, lead to large resections requiring reconstructive surgery with important functional implications. Today this aim can be achieved through the use of microvascular free flaps that have replaced classical local and regional flaps to ensure oncologic radicality on one hand, better functional and aesthetic results on the other.

In fact, quality of life has gained great interest in the last years, and has become a secondary endpoint of care, while survival is the main outcome for these patients. Starting from this observation, we focused on disease-specific survival (DSS), because the relatively advanced age and comorbidities of patients can create several problems when basing outcome only on overall survival. We analysed a cohort of 130 patients treated with reconstructive surgery affected by oral cancer from 2005 to 2013 and correlated survival to clinical and pathological parameters.

Materials and methods

Patients

The retrospective cohort consisted of 130 patients affected by oral cancer; all underwent surgical treatment between 2005 and 2013 at the Department of Head and Neck Surgery - Otolaryngology/Department of Plastic and Reconstructive Surgery, Catholic University of Sacred Heart. 88% of the patients were affected by oral squamous cell carcinoma (OSCC). The main clinical characteristics of our patients are shown in Table I. Preoperative head and neck CT and MRI (to establish clinical staging and therapeutic planning), total body PET-CT (in case of relapse/persistence of disease), colour Doppler ultrasound of neck vessels and free-flap donor vessels (to evaluate anatomy and calibre of vessels and perforator anatomy in case of perforator flaps) were performed for each patient.

The type of oncologic resection and reconstruction, as well as length of stay in the intensive care unit and recipient/donor site postoperative complications were also recorded.

All patients underwent radical compartmental surgery followed by immediate microvascular flap reconstruction. Because of the correlation between the thickness of the primary tumour and the risk of nodal metastasis, we performed selective bilateral neck dissection in all patients who presented a depth of tumour invasion > 3 mm, or a locally advanced stage (T3-T4) with N+ at presentation. Adjuvant radiotherapy was performed in case of positive margins, T4 status, N status >1 and extracapsular spread. Following the NCCN guidelines, we respected the ≤6 week interval between resection and post-operative RT and used a typical regimen based on a three field method including bilateral parallel opposed fields to the primary site and upper neck. We generally administered 60-66 Gy (2 Gy daily fraction 5 days per week) for irradiation of the primary site and neck in case of involved nodal stations, and 44-64 Gy (1.6-2.0 Gy daily fraction 5 days per week) for the neck in case of uninvolved nodal stations.

Recurrence was evaluated as local (if involving only the oral cavity relative to the primary tumour), regional (if involving only the neck) and loco-regional (if involving both the primary site and neck). To confirm recurrences, we used biopsy, CT or MRI and generally PET-CT.

Statistical analysis

Data were analysed with statistical software (SPSS 21.0 for Windows; SPSS, Inc., Chicago, IL). DSS curves were obtained using the Kaplan-Meier method. Log-rank test and generalised Wilcoxon test were used to investigate the most important prognostic factors on 5-year DSS. A Cox proportional hazards model was constructed to provide hazard ratios for individual variables. A $P$ value <0.05 was considered statistically significant.

Results

There were 46 (35.4%) women and 84 (64.6%) men in the sample with a mean age of 58.5 years ± 12.04 (range 26 to 83 years). On a total 130 patients, 119 received primary surgery in our department; 13 received salvage surgery for persistence/recurrence of disease; 11 underwent primary surgery in different hospitals and were referred to us for treatment of recurrence with reconstructive surgery. As shown in Table I, 58 patients (44.6%) received an ALT flap, 28 (21.5%) a fibula flap, 18 (13.9%) a FFR flap, 14 (10.8%) a DIEP flap, 6 (4.6%) a TRAM flap and 1 (0.8%) a VRA frame reconstruction. Five patients (3.8%) underwent reconstruction with a chimeric flap, defined as a combined composite flap used in special cases in which we had the need to reconstruct, in addition to a bone defect, an extensive cutaneous or mucosal defect.

At the end of the follow-up period, on June 2013, (average 33.4; range 2 to 205 months) 36 patients had died, 33 for the disease and 3 for other causes. We observed a 5-year DSS of 67.8% (± 4.9% SE) (Fig. 1). Univariate Kaplan-Meier analysis revealed statistically significant relationships between DSS and T (p = 0.026) and N (p = 0.0001) status, clinical stage (p = 0.007), margins of resection (p = 0.001), extracapsular spread (p = 0.005), recurrence of disease (p = 0.00002) and treatment modality (p = 0.004). Results are shown in Table II. Kaplan-Meier survival curves by different variables are shown in Figure 2.

On multivariate Cox regression analysis, the same variables showed a significant relationship with DSS, and in particular N stage (HR 2.2; p = 0.0001), margins of resec-
tion (HR 2; \( p = 0.0001 \)) and recurrence of disease (HR 5.3; \( p = 0.00001 \)). Results are summarised in Table III.

Flap complications

Nine patients experienced major complications after sur-
### Table II. Kaplan-Meier analysis: relationship between variables and survival.

| Variables                      | No. patients (%) | 5 year DSS (±S.E.) | Mean survival time (mo) (95% CI) | p value |
|--------------------------------|------------------|--------------------|----------------------------------|---------|
| **Gender**                     |                  |                    |                                  |         |
| Male                           | 84 (64.6%)       | 63.9% (5.9%)       | 75.9 (64-87)                     | 0.20    |
| Female                         | 46 (35.4%)       | 75.4% (8.4%)       | 159.7 (130-188)                  |         |
| **Age**                        |                  |                    |                                  | 0.88    |
| Mean                           | 58.5 (±1.05 S.E.)|                    |                                  |         |
| <50                            | 36 (27.7%)       | 62.3% (3.6%)       | 76.7 (60-93)                     |         |
| ≥50                            | 94 (72.3%)       | 68.1% (5.4%)       | 148.8 (128-269)                  |         |
| **Primary site**               |                  |                    |                                  | 0.62    |
| Tongue                         | 56 (50%)         | 73% (6.1%)         |                                  |         |
| Floor of mouth                 | 29 (22.3%)       | 68.5% (9.5%)       |                                  |         |
| Retromolar trigone             | 12 (9.2%)        | 56.6% (17%)        |                                  |         |
| Gum                            | 8 (6.2%)         | 37.5% (17.1%)      |                                  |         |
| Buccal mucosa                  | 3 (2.3%)         | 50% (34%)          |                                  |         |
| Palate                         | 7 (5.4%)         | 53.3% (24.8)       |                                  |         |
| Mandible                       | 3 (2.3%)         |                    |                                  |         |
| Lip                            | 3 (2.3%)         | 66.7% (27.2%)      |                                  |         |
| **Histology**                  |                  |                    |                                  | 0.36    |
| Squamous cell carcinoma (SCC)  | 115 (88.4)       | 65.2% (5.3%)       |                                  |         |
| Adenoid cystic carcinoma       | 7 (5.4)          | 100%               |                                  |         |
| Other                          | 8 (6.2)          | 83.3% (15.2%)      |                                  |         |
| **T status**                   |                  |                    |                                  | 0.026   |
| T1                             | 10 (7.7%)        | 100%               |                                  |         |
| T2                             | 45 (34.6%)       | 84.9% (5.7%)       |                                  |         |
| T3                             | 30 (23.1%)       | 64.7% (10.6%)      |                                  |         |
| T4                             | 45 (34.6%)       | 47.5% (9.2%)       |                                  |         |
| **N status**                   |                  |                    |                                  | 0.0001  |
| N0                             | 52 (40%)         | 87% (5.7%)         | 98.8 (88-108)                    |         |
| N1                             | 31 (23.9%)       | 66.2% (10.2%)      | 66.9 (53-80)                     |         |
| N2                             | 45 (34.6%)       | 54% (8.1%)         | 115.6 (85-146)                   |         |
| N3                             | 2 (1.5%)         | 0%                 | 11.5 (0-28)                      |         |
| **Clinical Stage**             |                  |                    |                                  | 0.007   |
| I                              | 5 (3.8%)         | 100%               |                                  |         |
| II                             | 20 (15.4%)       | 93.3% (6.4%)       |                                  |         |
| III                            | 33 (25.4%)       | 80.1% (8.3%)       |                                  |         |
| IV                             | 72 (55.4%)       | 54.2% (6.9%)       |                                  |         |
| **Type of flap**               |                  |                    |                                  | 0.055   |
| ALT                            | 58 (44.6%)       | 77.4% (6.1%)       |                                  |         |
| Fibula                         | 28 (21.5%)       | 68.3% (10.4%)      |                                  |         |
| FFRF                           | 18 (13.9%)       | 73.3% (17.6%)      |                                  |         |
| DIEP                           | 14 (10.8%)       | 30.6% (15.7%)      |                                  |         |
| TRAM                           | 6 (4.6%)         | 66.7% (19.2%)      |                                  |         |
| Chimeric Flap                  | 5 (3.8%)         | 30% (23.9%)        |                                  |         |
| VRAM                           | 1 (0.8%)         | 100%               |                                  |         |
| **Margin**                     |                  |                    |                                  | 0.001   |
| Positive                       | 19 (14.6%)       | 24.2% (10.5%)      | 35.3 (17-52)                     |         |
| Close                          | 14 (10.8%)       | 77% (11.5%)        | 71.4 (52-89)                     |         |
| Negative                       | 97 (74.6%)       | 76.5 % (5.5%)      | 161 (141-180)                    |         |
| **Extracapsular spread**       |                  |                    |                                  | 0.005   |
| Yes                            | 98 (75.4%)       | 46.7% (9.6%)       | 102.7 (66-138)                   |         |
| No                             | 32 (24.6%)       | 75.6% (5.4%)       | 88.3 (78-97)                     |         |
| Variables                        | No. patients (%) | 5 year DSS (±S.E.) | Mean survival time (mo) (95% CI) | p value |
|--------------------------------|------------------|--------------------|----------------------------------|---------|
| **Perineural invasion**        |                  |                    |                                  | 0.22    |
| Yes                            | 118 (90.8%)      | 58.3% (17%)        | 38.8 (23-54)                     |         |
| No                             | 12 (9.2%)        | 68.9% (5.1%)       | 146.3 (127-164)                  |         |
| **Mandible/Maxilla involvement** |                  |                    |                                  | 0.75    |
| Yes                            | 48 (36.9%)       | 60.5% (9%)         | 68.4 (55-81)                     |         |
| No                             | 82 (63.1%)       | 72.4% (5.5%)       | 151.7 (130-172)                  |         |
| **Recurrence**                 |                  |                    |                                  | 0.00002 |
| Yes                            | 47 (36.1%)       | 86.9% (4.1%)       | 97.9 (89-105)                    |         |
| No                             | 83 (63.9%)       | 38.4% (8.7%)       | 89.2 (58-120)                    |         |
| **Treatment modality**         |                  |                    |                                  | 0.004   |
| Surgery alone                  | 46 (35.4%)       | 90.1% (4.7%)       | 101 (91-110)                     |         |
| Surgery + RT/CT                | 84 (64.6%)       | 56.6% (6.4%)       | 122.9 (99-146)                   |         |
| **Lymph node dissection**      |                  |                    |                                  | 0.63    |
| Unilateral                     | 14 (10.8%)       | 57.9% (19.9%)      |                                 |         |
| Bilateral                      | 114 (87.7%)      | 67.5% (5.2%)       |                                 |         |
| No                             | 2 (1.5%)         | 100%               |                                 |         |

*According to UICC's TNM Sixth Edition.

Fig. 2. Kaplan-Meier survival curves by: A, Tumour size (p = 0.026); B, N status (p = < 0.0005); C, Clinical Stage (p = 0.007); D, Margins of resection (p = 0.001); E, Extracapsular spread (p = 0.005); F, Recurrence (p = < 0.0005); G, Treatment modality (p = 0.004).
surgery (9/130; 6.9%). Five patients had total flap failure for venous thrombosis (5/130; 3.8%); one of these was saved after vascular re-exploration, and the other four required a second flap. Three patients had exposure of osteoplastic plates and one patient had salivary fistula. The majority of these complications occurred when a fibula flap was used for reconstruction (6 cases) and 2 of 8 complications occurred when using other types of flaps.

Discussion

Oral carcinoma still remains a neoplasm with poor prognosis, especially for advanced stage tumours. The local control rate extends from 95% of T1-T2 lip carcinoma to 20% of T4 tongue and retromolar trigone cancer. In the past 20 years, the contribution of plastic and reconstructive surgery has resulted in a breakthrough in the treatment of these tumours, and in particular for reconstruction of large and complex tissue defects. As demonstrated by De Vicente et al., free flap surgery leads to a trend toward better survival than loco-regional flap, primary closure or skin grafts; this is because the chance to re-establish anatomical and functional continuity guarantees genuine oncological radicality, improving, on the other hand, quality of life. The study by Marchetti et al. showed an overall 5-year survival rate of 41.9% in a cohort of 42 oral cancer patients treated by microvascular flap reconstruction, while De Vicente et al reported a 5-year survival rate of 58.6% in the “free flap group” (49 patients). The best results were achieved by Rogers et al.; with an overall 5-year survival of 51% (2% SE), they obtained a 5-year DSS of 70% (3% SE). In our experience, we obtained a DSS of 67.8% (4.9% S.E.). Results from statistical analysis highlight the role that some of the variables we considered play in influencing prognosis. Some of these, such as tumour size (expressed by pT stage), presence of lymph node metastasis, extracapsular spread and recurrence of disease are well known prognostic indicators for survival of oral cancer patients, and our results are in agreement with the findings in the literature. Other variables which, in our series, were shown to influence the survival are treatment modality and involved margins of resection. Moreover, the relationship between these prognostic indicators and DSS was statistically significant. These findings are not surprising: in fact, patients needing adjuvant radio/chemotherapy are usually affected by advanced stage disease (T4 stage, lymph node metastasis > N1, presence of extracapsular spread or involved margins of resection) or a particularly aggressive neoplasm (in fact, only 10% of patients suffering a relapse of disease underwent surgery alone), and in our opinion this is the reason for the poor prognosis. Our study sample included a large percentage of patients affected by stage III-IV disease; 14.6% and 10.8%, respectively, had involved and close margins of resection. Analysing the corresponding Kaplan-Meier curve, it is possible to appreciate that patients with negative and close margins showed approximately the same trend of survival, in contrast to those with positive margins, which are characterised by a much more unfavourable prognosis.

Microvascular flap surgery could ideally lead to better control of disease, because the possibility of bridging extended tissue defects can push surgeons to perform more aggressive resections to achieve a truly oncological radical result, especially in light of the close correlation between prognosis and disease-free resection margins.

Table III. Cox regression analysis.

| Variables                        | χ² | SE  | Exp(B) | 95% confidence interval | p value |
|----------------------------------|----|-----|--------|-------------------------|---------|
| Gender                           | 1.8| 0.40| 0.58   | 0.26                    | 1.28    | 0.18   |
| Age                              | 0.1| 0.37| 1.15   | 0.55                    | 2.38    | 0.7    |
| Primary site                     | 1.1| 0.08| 1.09   | 0.92                    | 1.29    | 0.28   |
| Histology                        | 1.3| 0.58| 0.51   | 0.16                    | 1.64    | 0.26   |
| T status                          | 11.6| 0.21| 1.98   | 1.31                    | 3.01    | 0.001  |
| N status                          | 15.5| 0.21| 2.24   | 1.46                    | 3.43    | 0.0001 |
| Clinical stage*                  | 11.4| 0.35| 3      | 1.49                    | 6.03    | 0.002  |
| Type of flap                     | 4.8 | 0.09| 1.24   | 1.02                    | 1.50    | 0.03   |
| Margins                          | 15.7| 0.19| 2.04   | 1.40                    | 2.97    | 0.0001 |
| Extracapsular spread             | 9.2 | 0.35| 2.77   | 1.39                    | 5.52    | 0.004  |
| Perineural invasion              | 1.1 | 0.53| 0.56   | 0.19                    | 1.60    | 0.28   |
| Mandible/Maxilla involvement     | 0.4 | 0.35| 1.26   | 0.63                    | 2.51    | 0.5    |
| Recurrence                       | 23  | 0.39| 5.35   | 2.48                    | 11.54   | 0.00001|
| Treatment modality               | 9.5 | 0.53| 4.50   | 1.58                    | 12.82   | 0.005  |
| Lymph node dissection            | 0.4 | 0.53| 0.68   | 0.24                    | 1.96    | 0.48   |

*According to UICC TNM Sixth Edition.
This hypothesis has already been advanced by Hanasono 32 and reinforced by the data of De Vicenzo 26. As previously noted, in our series 19/130 patients (14.6%) had involved margins and 47/130 patients (36.1%) suffered recurrence of disease. Multivariate Cox backward logistic regression model demonstrated an influence of these two variables on patient survival (HR = 1.75 for margins of resection and HR = 4.63 for recurrence of disease; p = 0.003 and 0.0001 respectively). This result unfortunately deviates from those obtained by the authors mentioned above whom found positive margins in 7% and 8.2% of microvascular group patients, respectively 32,26. To explain this finding, we have to underline that the majority of patients with positive resection margins underwent microvascular flap surgery during the first years after the introduction of this technique in our surgical practice. Over the following years, the trend has shown a marked improvement, and in our opinion this result could be explained by looking on one hand at the enhancement of our reconstructive technique, and on the other at the increased confidence of highly aggressive surgery dismissing the mentality of a resection “cut on reconstruction”, in favour of an ablation which aims only to achieve oncological radicality 33,34.

Furthermore, during tumour resection not only of the tongue, but also in other sites of the oral cavity, we adopted the principles of compartmental surgery which advocate removal of compartments (anatomic-functional units) containing the primary tumour, eliminating the disease and potential muscular, vascular, glandular and lymphatic pathways of spread and recurrence 35. This could also explain the improvement of DSS observed in our series even if we had a large number of patients with advanced stages of disease.

Finally, the progressively increasing use of the anterolateral thigh perforator flap and the DIEAP-polygonal flap, which have become workhorses for head and neck soft tissue reconstruction, are associated with better results in terms of disease-free margins of resection, also because their use as an “on-site tailoring” flap instead of a “pre-marked” flap allows to tailor the flap at the end of the oncologic resection 36.

Conclusions
In conclusion, in our experience, reconstruction of oral cavity defects with microvascular flaps combined with compartmental surgery confirms that it can play an important role in increasing survival in oral cancer patients.

Acknowledgements
The authors would like to thank Dr Stefano Granieri for his important contribution.

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