

LARYNGOLOGY

Impact of resection margin status on oncological outcomes after CO₂ laser cordectomy

Impatto sui risultati oncologici dei margini di resezione dopo cordectomia laser CO₂

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SUMMARY

The management of positive resection margins in micro-endoscopic glottic laser surgery remains a controversial and critical point. This study aims to assess the impact of margin status after transoral laser surgery on local control, survival and organ preservation rates; the decision-making process and treatment options in cases with positive margins are also discussed. We retrospectively reviewed the clinical and histological records of 308 consecutive patients with primary early glottic carcinoma (T1a, T1b, selected T2) and treated with endoscopic laser cordectomy. Recurrence rates and survival related to margin status were analysed using the Kaplan-Meier method. Local relapses and disease-free-survival rates were significantly related to excision margin status ($p < 0.001$). In the T1a category ($n = 228$) no significant differences were observed in disease-free-survival ($p = 0.889$) and overall survival ($p = 0.426$) between patients submitted to further treatment (revision endoscopic surgery or radiotherapy) for positive excision margins and patients who were left untreated. In 20 of 24 (83%) patients with positive margins that were surgically re-excised, no residual carcinoma was detected. Margin status (mainly multifocal and deep positive margins) at first surgery was significantly related to the final organ preservation rate ($p < 0.001$). Margin status during laser cordectomy in early glottic cancer has a prognostic impact on local control of disease without compromising survival. Patients with multifocal and deep positive borders should be surgically retreated and strictly monitored to increase the organ preservation rates. Careful preparation and mapping of the surgical specimen enhances the accuracy of pathological examination by reducing the risk of overestimate positive margins.

KEY WORDS: CO₂ laser • Cordectomy • Early glottic carcinoma

RIASSUNTO

Le modalità di trattamento dei margini positivi dopo cordectomia endoscopica con laser CO₂ presentano aspetti critici e ancora controversi. Questo lavoro si propone in primo luogo di analizzare l'impatto dello stato dei margini positivi dopo cordectomia endoscopica sul controllo di malattia, sulla sopravvivenza e sulle percentuali di preservazione d'organo; secondariamente di discutere le strategie operative e le opzioni di trattamento nei pazienti con margini positivi. Sono stati analizzati retrospettivamente i dati clinici ed istologici di 308 pazienti consecutivi trattati per carcinomi glottici in stadio iniziale (T1a, T1b e T2 selezionati) mediante cordectomia endoscopica laser CO₂. Per l'analisi dei tassi di recidiva e di sopravvivenza è stato impiegato il metodo di Kaplan-Meier. Le recidive locali di malattia e la sopravvivenza libera da malattia correlavano in modo statisticamente significativo con lo stato dei margini di resezione ($p < 0,001$); le percentuali di sopravvivenza globale a 60 mesi risultavano essere pari al 90% per i margini negativi e all'81,4% per quelli positivi ($p = 0,27$). Nei casi con margini di resezione positivi appartenenti al gruppo T1 ($n = 228$) non sono state riscontrate differenze statisticamente significative, in termini di sopravvivenza libera da malattia ($p = 0,889$) e globale ($p = 0,426$), fra pazienti sottoposti a ulteriore trattamento (revisione chirurgica endoscopica o RT) e pazienti non trattati. In 20 dei 24 (83%) pazienti con margini positivi trattati mediante revisione chirurgica endoscopica non è stato riscontrato carcinoma residuo. Lo stato dei margini (principalmente di quelli profondi) dopo il primo intervento chirurgico risultava correlare significativamente con le percentuali di preservazione finale d'organo ($p < 0,001$). Lo stato dei margini dopo cordectomia laser CO₂ nei carcinomi glottici in stadio iniziale ha un impatto prognostico sul controllo locale di malattia senza compromettere la sopravvivenza. I pazienti con margini positivi multifocali e profondi devono essere sottoposti a revisione chirurgica e stretto follow-up per incrementare le percentuali di preservazione d'organo. È necessario allestire e mappare in modo molto scrupoloso gli specimen chirurgici al fine di ottimizzare la valutazione istopatologica e ridurre il rischio di sovrastimare i margini positivi.

PAROLE CHIAVE: Laser CO₂ • Cordectomia • Stadi iniziali del carcinoma glottico

Introduction

Transoral laser microsurgery (TLM) represents a minimally invasive approach that is widely accepted in early glottic cancer¹. Moreover, this endoscopic procedure can be easily repeated when positive margins are detected postoperatively or, in many cases, when local relapses occur².

While surgical margin status significantly impacts local control and survival in head and neck cancer³, the prognostic significance of positive resection margins after endoscopic laser surgery for early stage glottic cancer remains controversial. The high incidence (up to 50%) of positive neoplastic margins after laryngeal laser microsurgery reported in the literature may be due to the modality of laser dissection performed in narrow free tissue, especially in the glottic area, which is justified by anatomic and functional reasons^{2,4}.

The results of the several series reported up to now have not led to univocal interpretation on the significance of margin status since, in some of these, positive margins seem to determine a negative impact on local relapses, whereas in most studies they do not influence survival. The incidence of local recurrence after endoscopic laser cordectomies has been reported to range from 0 to 9.3% and from 14 to 50%, respectively, for negative and positive resection margins⁵⁻⁹.

In many series of TLM with positive/close margins at pathological examination, a high incidence (up to 80-90%) of cases with no residual disease in revision specimen has been reported^{1,9,10}. Neoplastic cells in revision specimen represent a prognostic factor for poor local control, rather than positive margins in the initial specimen¹. The low concordance between positive margins after primary laser cordectomy and pathological findings after revision surgery may be due to postoperative artifacts of surgical specimen. For all these conditions, the tissue specimens after TLM may be not fully representative of real extent of resection^{1,5}.

On these bases, herein we have retrospectively reviewed our series of 308 patients with primary early glottic cancer treated by TLM. The main aims were to correlate the status of resection margins with local control rate, survival and organ preservation, and to discuss the decision-making process and further treatment options in cases with positive margins. The methodological procedures and the pitfalls of pathological diagnosis are also analysed.

Materials and methods

Patients

Between 1990 and 2010 a total of 308 consecutive patients with early glottic carcinoma (T1a, T1b, selected T2) were

treated at the Department of Otorhinolaryngology, Head and Neck Surgery, University of Eastern Piedmont, Novara (Italy). All clinical and surgical records and histopathological reports were collected from the department's tumour registry and retrospectively reviewed. Demographics, tumour T stage, types of laser cordectomy and resection margin status were collected. There were 291 men and 17 women, with a mean age of 65.2 years (range 32-91).

Technique

All patients underwent TLM under general anaesthesia using a Sharplan CO2 laser (Acublade system) mounted on a Zeiss surgical microscope. A Mallinckrodt laser-flex tracheal tube with a double cuff was employed. Endoscopic laser cordectomy were graded according to the classification system proposed by the European Laryngological Society (ELS)¹¹, as follows: type I subepithelial (n = 9), type II subligamental (n = 32), type III transmuscular (n = 107), type IV total (subperichondral) (n = 102), type V extended (n = 58). Most glottic cancers were removed "en bloc", and a multi-bloc procedure was utilised in bulky tumours on rare occasions.

Inclusion criteria were: no previous curative laryngeal treatment and good endoscopic glottic exposure at micro-laryngoscopic examination. In many cases, tumour diagnosis was previously confirmed by biopsy; however, in recent years an excision-biopsy was systematically planned in superficial and favourable limited lesions (selected T1) in order to spare a surgical procedure and to avoid treatment delay. In the latter cases, an extensive and informed consensus on this type of diagnostic and therapeutic procedure was obtained. We excluded all cases with pT0 postoperative staging ("curative biopsy") from the study. A preoperative CT scan was systematically obtained in all glottic cancers except for early and superficial lesions limited to the middle third of the vocal fold. Intraoperative diagnostic examination included rigid endoscopy with 0° and 70° angles of view and, recently, a narrow band imaging system (NBI) for planning the extension of surgical resection.

Surgical specimens were three-dimensionally oriented and opportunely fixed on a plastic slab with fine needles to avoid excessive tissue contraction and distortion that could interfere with pathological assessment. The superficial and deep resection margins were marked with different coloured inks before formalin fixation (Fig. 1).

Resection margins were defined as positive if they were infiltrated by neoplastic tissue, and close if < 1 mm of free tissue between margins and tumour was present.

All surgical specimens with close or positive margins included in this study were systematically reassessed by an experienced pathologist to confirm margin status.

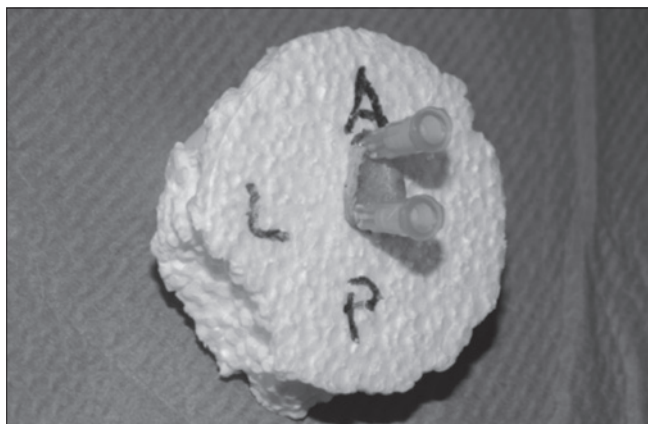


Fig. 1. Surgical specimen from laser cordectomy prepared for pathological examination: the deep (lateral) margin has been stained by yellow ink; A: anterior margin; P: posterior margin; L: lateral margin.

Follow-up ranged from 12 to 243 months (median, 68.3 months). Patients were examined with flexible video-laryngoscopy or rigid video-laryngoscopy every 1-2 months the first year and subsequently every 2-6 months depending on staging and margin status. During endoscopic follow-up, microlaryngeal examination was routinely planned if suspicious areas were observed.

Indications for adjuvant therapy in patients with positive surgical margins have changed over the years: until 2008 postoperative radiotherapy was performed in some cases ($n = 20$). At present, a second look laryngoscopy is preferred and planned within 4-6 weeks in deep and/or multifocal positive margins, whereas monthly endoscopic follow-up is proposed if a close margin or a single superficial margin is involved, under the condition that an intraoperative satisfactory excision is obtained.

Statistical analysis

Disease-free survival (DFS) was calculated from the date of cordectomy to the date of relapse or last follow-up. Overall survival (OS) was considered from cordectomy to death or last follow-up. Larynx survival was estimated from the date of cordectomy to the date of laryngectomy or last clinical examination. Observations were censored at 60 months. Survivals were calculated considering as variables the presence of positive/close margins at cordectomy and, in these cases, the site of margin involved (superficial vs deep), additional treatment performed on these patients, TNM staging and type of cordectomy.

Kaplan-Meier analysis was used to describe disease-free survival and overall survival in different clinical groups (Tis, T1 and T2 categories were analysed separately). Comparison of groups was carried out using the Log-rank

test, and a two-sided p value < 0.05 was considered statistically significant.

Results

According to the AJCC TNM staging system (2002), T clinical categories of the 308 endoscopic laser cordectomies were distributed as follows: 29 Tis (9.4%), 228 T1a (74%), 29 T1b (9.4%) and 22 T2 (7.2%). Most T1 lesions were treated with either a type III or a type IV cordectomy (110 and 107, respectively).

Of 102 primary cases (33.1%) with non-negative surgical margins detected at definitive pathological examination, 85 were clearly positive (both superficial and/or deep margins) and 17 were defined as close margins. Endoscopic revision surgery was performed in 24 of 85 cases (28.2%), all with multifocal and/or deep positive margins: in 20 of 24 of these, no residual carcinoma was detected (83%), whereas in the other 4 cases (17%) positivity was confirmed (Table I). In the other 20 cases (23.5%), postoperative radiotherapy was performed. In the remaining 41 of 85 cases in which a satisfactory resection was achieved and only one superficial positive margin was histologically detected, we used a “wait and see” strategy; accordingly, in these patients no further treatment but only strict follow-up was planned.

Local recurrences were diagnosed in 39 of 308 cases of TLM, and the overall recurrence rate was 12.6%; 23 of these relapses were found in patients with positive margins at first surgery and 16 in negative ones. Twenty-three of 102 primary cases with positive margins (22.5%) and 16 of 206 with free surgical margins (7.8%) relapsed.

Resection margin status was significantly associated with local recurrence and lower DFS ($p < 0.001$) for T1a, T1b and T2 categories, whereas OS at 60 months for negative and positive/close margins was 90% and 81.4% ($p = 0.27$, 95%CI), respectively (Fig. 2). The site of positive margins (deep vs. superficial) did not show significant differences in the rate of recurrence ($p = 0.99$) or OS ($p = 0.98$); at 60 months, OS was 72% and 85% for superficial and deep positive margins, respectively. On the contrary, a significant difference emerged between close/single superficial margins and multifocal/deep margins ($p < 0.001$). In the group

Table I. Histological findings of revision surgery cases ($n = 24$).

	Negative	Positive	Total
All margins	20	4	24
Deep margins *	11	3	14
Superficial margins **	9	1	10

* at least one deep margin involved at first surgery.

** only superficial margins involved at first surgery.

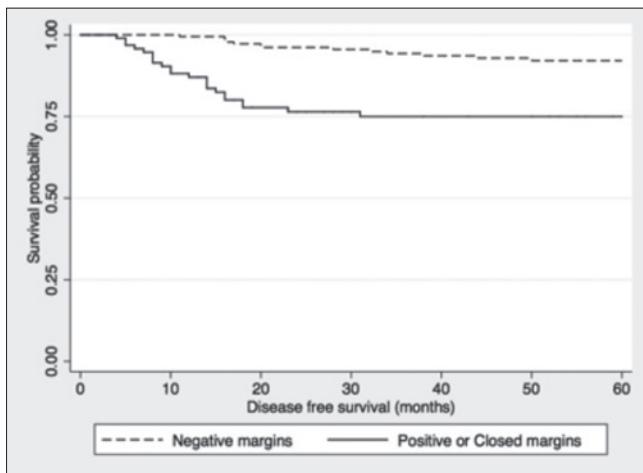


Fig. 2. Disease-free survival (DFS) according to margin status; the presence of positive and/or closed margins is negatively related to disease-free survival ($p < 0.001$). Kaplan-Meier method.

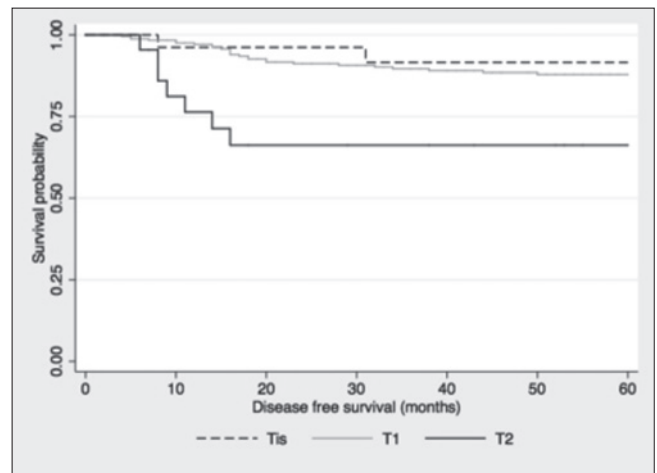


Fig. 3. Disease-free survival (DFS) according to T stage (Tis vs. T1 vs. T2); patients with T2 stage show worse prognosis ($p < 0.002$). Kaplan-Meier method.

of T1a patients ($n = 228$), no significant differences in rate of recurrences, DFS ($p = 0.889$), or OS ($p = 0.426$) were observed between patients submitted to further treatment (revision endoscopic surgery or RT) for positive excision margins at first surgery and patients who were left untreated. The type of laser cordectomy for T1 stage was not significantly related to either DFS ($p = 0.39$) or OS ($p = 0.0617$). TNM stage was significantly related to the rate of recurrence ($p = 0.002$), but did not negatively impact overall survival ($p = 0.316$) (Fig. 3). Distribution of recurrences by T stage is shown in Table II.

Recurrences were treated conservatively by repeated endoscopic laser surgery in 9 subjects and by supracricoid laryngectomy in one patient. Local control with laser alone was 89%. Twenty-four patients underwent salvage total laryngectomy for recurrence: in this group, surgical margins at first laser surgical procedure were positive in 15 cases (11 deep and 4 superficial) and negative in 9. In these patients, salvage treatment with chemo-radiotherapy was jointly discussed, but was decided against. The laryngeal preservation rate at 60 months was 90% (95.6% in negative margins group and 85% in close/positive margin

group, respectively). Margin status (mainly deep positive margins) at first surgery was significantly related to the final organ preservation rate ($p < 0.001$) (Fig. 4).

Of four cases with confirmed residual carcinoma after second-look surgery, 2 are alive without disease (one patient was submitted to a further endoscopic intervention for a local relapse) and 2 died for unrelated causes. In our series, 58 patients died, 7 of local recurrences (5 with positive and 2 with negative excision margins at first laser surgery) and 51 of unrelated causes; 14 patients were lost to follow-up.

Discussion

The presence of neoplastic tissue in resection margins is

Table II. Distribution of recurrences per T stage ($n = 308$).

	Cases (n)	Recurrences (n)	Recurrences %
Tis	29	3	10.3
T1a	228	25	11.0
T1b	29	4	13.8
T2	22	7	31.8
TOT	308	39	12.7

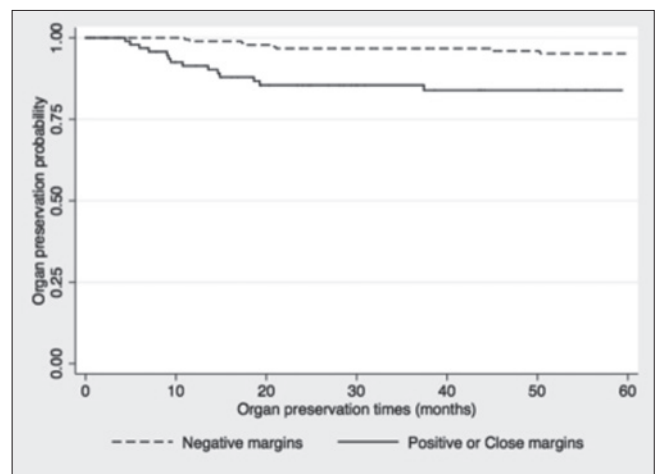


Fig. 4. The presence of positive margins is significantly related to failure in organ preservation ($p < 0.001$). Kaplan-Meier method.

usually known to be a negative prognostic factor in HN-SCC¹⁰. Anatomic and embryologic specificity of the glottic area and microsurgical magnification allows obtaining a successful oncological outcome even in cases of early laryngeal cancer with limited free margins. In fact, whereas for other head and neck surgical specimens clear margins of at least 5 mm are considered oncologically adequate, a 3 mm space of free tissue from the neoplastic front is enough to achieve good oncological results in conservative laryngeal surgery^{12,9}. The superficial and exophytic growth pattern of most glottic cancers, often sparing muscle, and the absence of lymphatic drainage in the glottic area justifies this surgical approach.

The type of TLM and extension of muscle resection should be tailored to the individual patient in relation to site and depth of neoplastic infiltration, in order to spare most healthy tissue and obtain better phonatory results. Thus, especially in superficial early glottic cancers, the laser excision can be adapted individually in respect of the oncological criteria⁸. An excisional biopsy, with diagnostic and therapeutic purpose, should be recommended in suspected superficial, limited glottic cancers to avoid additional surgical procedures and to limit the risk of overtreatment. Indeed, after performing a laser cordectomy for glottic cancer histologically confirmed by biopsy, the pathologist sometimes does not find any residual cancer in the surgical specimen. Such negative cordectomies were identified in 32.6% of early glottic cancers treated by TLM and previously biopsied⁴.

In our series, we evaluated the margin status of specimens by strictly applying the pathological criteria described above, and found clearly positive margins in 27.6% of cases, whereas close margins were present in another 5.5%; this result is similar to other studies, since in the literature positive margins after TLM are reported in 10-50% of cases¹¹²⁻¹⁴. The clinical significance of positive or close margins in surgical specimens of laser cordectomy is still debated: local relapses after TLM in early glottic cancer have been reported in many studies, ranging from 6% to 22%¹³⁻¹⁸. However, overall survival does not seem to be affected by either margin status at first surgery or by modality of treatment of positive margins (revision surgery vs. radiotherapy). These observations may be explained by the fact that local recurrences after TLM are frequently detected in relative early stages and can be successfully treated, thereby achieving high survival rates. However, margin status of surgical margins can negatively impact the laryngeal preservation rate¹. For our patients, local relapses and DFS were significantly correlated with the margin status, as well as with the organ preservation rate. Similar results were obtained by Ansarin et al. who analysed, in a multivariate model, the results of 8-year follow-up in relation to margin status (n = 274); pa-

tients with close and positive margins, not further treated with a second resection nor adjuvant RT, had a greater risk of recurrence (hazard ratio, 2.53; p = 0.06) than patients with negative margins¹⁹. In contrast, Michel et al., in a series of 64 patients retrospectively analysed after TLM for T1a glottic carcinoma, did not observe any significant difference in recurrence-free or OS in relation to the status of resection margins⁹.

The site of positive resection margins (deep or superficial) may also influence surgical outcome, as reported in a large series of 595 glottic cancers treated with TLM. The authors emphasised the importance of a meticulous preoperative examination and complete removal of the tumour at the first surgical procedure because endoscopic revision for positive deep margins may be not sufficient to obtain an adequate local control⁸. Recently, a retrospective study has demonstrated that post-resection CO2 laser photocoagulation of surgical close or positive superficial margins significantly decreases the rate of local recurrences after endoscopic cordectomy²⁰.

In other series, an intraoperative procedure on frozen sections has been applied to evaluate resection margins: by this technique it has been demonstrated that involvement of the margins during the primary resection was predictive for poor OS in 75 consecutive patients²¹. A high negative predictive value (95%) of frozen sections in a series of 97 patients treated by TLM with the Acublade system has also been reported²². However, this method is burdened with a high false negative rate²³. The application of frozen sections to evaluate the status of resection margins is debatable and has not been applied by all groups¹⁹. In our experience, this tool was not too effective because of the thermal effects on the specimen, leading to difficult interpretation of morphologic findings even if, more recently, the Acublade system has reduced this problem.

On the other hand, no residual carcinoma was found in 83% of our patients (24 cases) submitted to revision surgery for positive margins. In many series of TLM a high incidence of cases with no residual disease in specimen at second look surgery has been reported: for instance, Jackel demonstrated that only 70 of 382 patients (18%) had confirmed positive neoplastic margins at revision surgery¹. The definition of false positives for these cases may be inappropriate, as the immune system of the host is functionally able to attack and destroy small fields of neoplastic cells²⁴. This may also explain the relatively high frequency of cases with a diagnosis of squamous carcinoma on biopsy, and the absence of tumour on the subsequent TLM⁴.

Nonetheless, it should be assumed that the presence of residual tumour on the margins of TLM is due, at least in a proportion of cases, to postoperative modifications and

artifacts of the surgical specimen, such as shrinkage, inadequate orientation and mapping and thermal effects of tissue coagulation. Since these pitfalls may result in pathological misinterpretation and in over-diagnoses of positive margins, we have applied a standard procedure to treat the surgical specimen for pathological analysis: a mild stretching with needles on a rigid frame and tridimensional mapping with inks is useful to reduce post-resection shrinkage of excised tissues. Of course, strict cooperation between surgeons and pathologists is mandatory.

The management of positive or close resection margins in endoscopic cordectomy remains a controversial and critical point. The options discussed in the literature vary from planned early revision endoscopic surgery to complementary radiotherapy or only strict endoscopic surveillance. According to most authors, whenever retreatment is planned, revision surgery should be preferred^{8,20}. Deep recurrences are difficult to detect early even with close endoscopic follow-up, and negatively impact on chances for conservative treatment in case of relapses. For this reason, systematic re-excision in all positive or suspected deep positive margins should be suggested. If a single superficial margin is positive and laser excision was satisfactorily achieved, a strict endoscopic follow-up may be proposed, reserving revision surgery only in case of suspected neoplastic persistency, as previously reported^{25,26}.

Conclusions

The present study shows that positive margins after TLM for early glottic cancer has a prognostic impact on local control and organ preservation without compromising survival. Careful preparation and mapping of the surgical specimen enhances the accuracy of pathological examination by limiting over-diagnoses of positive margins. Decision-making process in positive margins cases (revision surgery, radiotherapy, or no further treatment) should also be based on the surgeon's experience and intraoperative judgment. Multifocal and deep positive margins after endoscopic laser cordectomy should be surgically verified and subsequently strictly monitored in order to increase local control and organ preservation rates.

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