Research Article

Concurrent Chemoradiotherapy Followed by Adjuvant Chemotherapy with Cisplatin for Advanced Head and Neck Squamous Cell Carcinoma.

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Abstract

Background: Concurrent chemoradiotherapy (CRT) is the most effective approach in controlling advanced head and neck cancer. Cisplatin is the most extensively cytotoxic agent investigated concurrently with radiation therapy as well as in neoadjuvant and adjuvant setting, so we started this study to confirm the efficacy of concurrent chemoradiotherapy followed by three cycles of adjuvant chemotherapy (cisplatin) in treating patients with locoregional advanced head and neck cancer. **Patients and Methods:** Between April ٢٠١٠ and November ٢٠١١, ٣٠ patients with advanced head and neck squamous cell carcinoma were treated at Minia Oncology Center with radical radiotherapy (٧٠ Gy/٣٥F/٧weeks) with three cycles of concurrently Cisplatin (١٠٠mg/m^{٢}) administered on day ١, ٢٢, ٤٣ of radiotherapy followed by three cycles of adjuvant chemotherapy (Cisplatin) with the same dose every ٣ weeks. All patients were assessed for response immediately after the concomitant phase and at ٢ months after completion of treatment. Follow up was maintained for a range from ١٠-٤١ months. Immediate locoregional control, treatment compliance, pattern of failure, toxicity profile, disease free and overall survival rates were estimated. **Results**: The median age of our patients was ٥٥.٥ years (range ٢٢-٦٦ years). Twenty one patients were males, with male to female ratio of ٢.٣:١.The majority of our patients (٤٦٪) had a primary tumor of the larynx. About (٦٣٪) had stage III disease. The planned dose of radiotherapy was completed in ٨٠٪ of patients, and ٧٠٪ completed the three cycle of adjuvant chemotherapy. Mucositis and neutropenia were the commonly recorded side effects. ORR (CR+PR) was ٨٦.٧٪, ٣ patients went into CR after the first phase of treatment. Another ١١ patients were turned into CR after the adjuvant phase. During the period of follow up, ١٨ patients relapsed (locoregional only no systemic relapse). The estimated ٢ year DFS was ٣٣.٣٪ and the estimated ٢ years OAS was ٨٩.٦٪. **Conclusion:** Concurrent chemoradiotherapy has produced improved results in patients with advanced head and neck cancers concerning locoregional control, disease free survival and overall survival more than radiotherapy alone, however more was achieved, especially concerning reduction of distant failure by addition of adjuvant chemotherapy.

Key Words: Head and Neck cancer, Cisplatin, Concurrent chemoradiotherapy

Introduction

Approximately ٤٠,٠٠٠ patients are newly diagnosed annually with squamous cell carcinoma of the head and neck (excluding skin cancer) in the United States. Approximately one third of these patients are women. Nearly ٦٠٪ of the head and neck cancer patients present with locally advanced, but non metastatic disease. Locoregional failure constitutes the predominant recurrence pattern, and most fatalities result from uncontrolled local and/or regional disease.[١]

Radiotherapy alone has long been the standard nonsurgical therapy for locally advanced disease. Even with the most effective RT regimens result in local control rates of ٥٠٪-٧٠٪ and disease-free survivals (DFSs) of ٣٠٪-٤٠٪. This circumstance has stimulated the investigation of treatments combining RT and chemotherapy. Most randomized clinical trials show the superiority of combined radiotherapy and chemotherapy to RT alone for the treatment of locally advanced HNC. Randomized

comparisons of concurrent chemoradiation (CRT) versus induction chemotherapy followed by radiotherapy alone are few but confirm that the former strategy is superior. Concurrent therapy clearly constituted the most effective means of larynx preservation and provided the best disease control.(٣)

Given that concomitant CRT increases locoergional control, and thereby avoids surgical resection of important anatomical structures, it was postulated that CRT may offer superior organ preservation in comparison to surgery, radiation, or sequential chemotherapy and radiation. Initially, two trials using sequential chemotherapy and radiation in comparison to surgery with adjuvant radiation reported improved organ preservation with no difference in survival. (٣)

The survival benefit of adding neoadjuvant or adjuvant chemotherapy to concurrent chemoradiotherapy for locoregional advanced head and neck cancer is currently investigated. The US intergroup trial was the first randomized study to show significant survival benefit by adding cisplatin (CDDP) concurrent with RT followed by adjuvant CDDP and fluorouracil (FU). A ٢٥٪ improvement in the ٢ years overall survival (OS) rate compared to RT alone was demonstrated in the initial report(٤)

Moreover an updated analysis of survival figures revealed a continued improvement of the ٥ years disease free, overall survival and improvement in the distant metastasis control as well.(٥)

Patients and Methods

Between April ٢٠١٠ and November ٢٠١١, ٣٠ patients with advanced head and neck squamous cell carcinoma were treated at Minia Oncology Center with radical radiotherapy (٧٠ Gy/٣٥F/٧ weeks) with three cycles of concurrently Cisplatin (١٠٠mg/m^{٢}) administered on day ١, ٢٢, ٤٣ of radiotherapy followed by three cycles of adjuvant chemotherapy (cisplatin) with the same dose every ٣ weeks. The protocol was approved by the ethical committee and informed consents had been obtained from all patients.

Patients age >١٨ years and <٧٥ years with Eastern Cooperative Oncology Group performance status of ٠ or ١, and who had measurable histologicaly confirmed stage III or IV but M٠, squamous cell carcinoma of the larynx nasopharynx , oropharynx, hypopharynx, tonsil or oral cavity and were previously untreated were eligible for this trial. Patients were required to have adequate blood count, renal and hepatic functions. The disease was staged according to the ٢٠١٠ classification of the American Joint Committee on cancer.

Exclusion criteria included: sever medical illness, other active malignancy in the last ٥ years, previous chemotherapy or radiotherapy, distant metastasis and surgery other than biopsy or tracheostomy.

All patients underwent staging work up including physical examination, complete blood work, chest x-ray, abdominal ultrasound, computed tomography or magnetic resonance imaging of head and neck. Additional tests include fiberoptic triple endoscopy, bone scan, and dental evaluation.

All patients were planned to receive a full course of radiotherapy to a dose of ٧٠ Gy (١.٨-٢ Gy/fraction) using ٦-MV linear accelerator. All fields were treated once daily, ٥ times a week. Radiotherapy started with two lateral opposing facialcervical fields to cover the primary tumor and neck lymph nodes to a dose of ٤٠ Gy. After ٤٠ Gy, to avoid further irradiation to the spinal cord, the posterior border of the lateral fields was displaced anteriorly. Additional ٢٠ Gy was delivered to the reduced upper lateral fields followed by another ١٠ Gy boost to primary lesion, and the posterior neck nodes was supplemented with ١٠ Gy (electron beam therapy) if it was negative and ٢٥-٣٠ Gy if it has positive nodes. The lower neck and suprcalvicular fossae were treated with an anterior field to ٥٠ Gy.

Patients were scheduled to receive three cycles of concurrent cisplatin (١٠٠mg/m^{٢} i.v. infusion) administered on day ١, ٢٢, ٤٣ of radiotherapy. Subsequently a further ٣ cycles of adjuvant chemotherapy comprising cisplatin (١٠٠mg/m^{٢} as ٢ hours i.v. infusion) repeated every ٣ weeks. Treatment modifications were carried out according to the following scheme: CDDP was omitted for a cycle during the concurrent RT phase if the minimum hematologic criteria were not met (absolute neutrophils count > ١,٠٠٠/μL

and platelet count > ١٠٠,٠٠٠/μL). During the adjuvant phase, deferment of the chemotherapy by up to a maximum of ٢ weeks was allowed if the same hematologic criteria were not met. Chemotherapy was also discontinued in the event of patient refusal, physician's decision for fear of RT compromise and unacceptable toxicities such as severe sepsis or renal impairment. Every effort was taken not to delay or break the course of RT.

All patients were assessed for response immediately after the concomitant phase and at ٢ months after completion of treatment. This assessment includes physical examination, CT scan or MRI of the primary and neck nodes. Endoscopy and biopsy was performed from any suspicious lesions.

Patients were followed clinically on monthly base for the first year and every three months from the second year. Radiological evaluation by CT Scan or MRI of the primary and neck nodes, as well as chest X-ray were performed annually or whenever there is suspicious of tumor recurrence, while abdominal ultrasound and bone scan were performed whenever there was a suspicious of distant metastasis.

Statistical analyses were performed using SPSS ١٥ software. Disease free survival and overall survival estimates were calculated according to Kaplan- Meier methods. Overall survival (OS) was defined as the interval from day one of treatment to either time of death or last visit. Progression-free survival (PFS) was calculated from day one of treatment to either death or diagnosis of recurrence or last visit. Objective response rate (ORR) could be defined as the proportion of patients whose best response was either partial or complete response (PR+CR).

Results

Between April ٢٠١٠ and November ٢٠١١ a total of ٣٠ patients were recruited onto study. Data collection was done Nov ٢٠١٣ with a follow up ranged from ١٠ to ٤١ months with median follow up time of ٢٦ months for surviving patients. Patient characteristics, primary site distribution, and primary and nodal staging are shown in table ١.

Patient and tumor characteristics:

The median age of our patients was ٥٥.٥ years (range ٢٢-٦٦ years). Twenty one patients were males, with male to female ratio of ٢.٣:١. The majority of our patients (٤٦%) had a primary tumor of the larynx. About (٦٣٪) had stage III disease. (Table ١).

Table ١ : patient's and tumor characteristics

Characteristics	No of Patients	%
Sex		
Male	٢١	٧٠
Female	٩	٣٠
Age, years		
Median	٥٥.٥ years	
Range	٢٢-٦٦ years	
Primary site of the tumor		
Nasopharynx	٦	٢٠
Hypopharynx	٣	١٠
Larynx	١٤	٤٦.٧
Oropharynx	٥	١٦.٧
Oral cavity	٢	٦.٧
Stage		
Stage III	١٩	٦٣.٣
Stage IV	١١	٣٦.٧

Treatment Compliance

Fifty percent of our patients fully complied with the treatment protocol. Fifteen out of ٣٠ patients were deviated during the concomitant CRT phase of treatment. Protocol deviation for the RT component included ٤ patients who received a total RT dose of no more than ٦٨ Gy and ٩ patients who had a gap during the radiotherapy treatment of more than one week and ٢ patients not complete RT. (table ٢).

Table ٢ : Compliance to radiotherapy

Radiotherapy	No.	%
Completed uninterrupted to full dose	١٥	٥٠
Not completed	٢	٦.٧
Completed with gap to full dose	٩	٣٠
Completed with gap and under dose	٤	١٣.٣

Nine patients had a reduced number of chemotherapy cycles during the adjuvant phase of the trial, two of them completed the concomitant CRT phase of treatment. This reduction in the number of adjuvant cycles was secondary to treatment toxicity (٨ patients) or patient refusal (one patient).

Treatment toxicity

For hematologic toxicity, the incidence of severe neutropenia was higher during the adjuvant phase of treatment than during CRT phase (١٠٪ v ٦٪, respectively), anemia also has the same incidence. On the other hand for none hematological toxicity, the incidence of oropharyngeal mucositis was significantly higher in the CRT phase of treatment (٣٠% in CRT v ٣٪ in adjuvant phase).

Pattern of failure:

Regarding pattern of failure after treatment, local failure (site of tumor) was happened in ١١ (٣٦.٧٪), LN failure in ٤ (١٣.٣٪), and LN with local failure in ٣ (١٠٪), No failure occurred in ٩ (٣٠٪) and no distant metastasis is reported.

Patient outcomes

All patients were evaluated for efficacy. ORR (CR+PR) was ٨٦.٧٪; where all patients were assessed for response, ٣ patients went into complete remission (CR) immediately after the concomitant CRT phase of treatment. ٢٣ patients achieved partial response (PR), however ١١ of them were turned into CR after the adjuvant phase of treatment, ٢ patients show stationary disease and two progressed in the primary site and one of them develop tracheo-oesphageal fistula. (Table ٣,٤).

Table ٣: Patient Outcomes

	Criteria	No.	%
Immediate response	CR after CRT	٣	١٠
	CR after adj. T	١٤	٤٦.٧

Table ٤: objective tumor response rate after the ٢ phases of treatment

Response	No. (n=٣٠)	Percent
Objective response rate	٢٦	٨٦.٧
Complete response	١٤	٤٦.٧
Partial response	١٢	٤٠
Stable disease	٢	٦.٧
Progressive disease	٢	٦.٧

Progression free survival and overall survival:

With a median follow up time of ٢٦ months for surviving patients range: (١٠-٤١ months). The median disease free survival (DFS) was ١٥ months (٩٥٪ CI: ١٢.٤-١٧.٥). and the estimated ٢ year DFS was ٣٣.٣%. The median overall survival (OAS) was ٢١ months (٩٥٪ CI: ١٩-٢٣.٥) and the estimated ٢ years OAS was ٨٩.٦% as seen in the Kaplan – Meier disease free survival and overall survival curves shown in figure ١& ٢. Eighteen patients out of the twenty six patients who achieved objective response had recurred or progressed at a median of ١٢.٥ months (range: ٥-٢٢ months), and ٥ patients out of ١٤ who achieve CR recurred at a median of ١٤ months (range:١٢-٢٢ months). One of two patients with SD progressed at ١٠ months and he underwent salvage surgery and he was still alive and disease free at last follow up, while the other patient had not progressed at last follow up.

Table ٥: Two year survival

Criteria		No. (n=٣٠)	Percent
Two year survival	(n=٢٧) Disease free	٩	٣٣.٣٪
	Overall ٢ year survival	٢٧	٨٩.٦٪

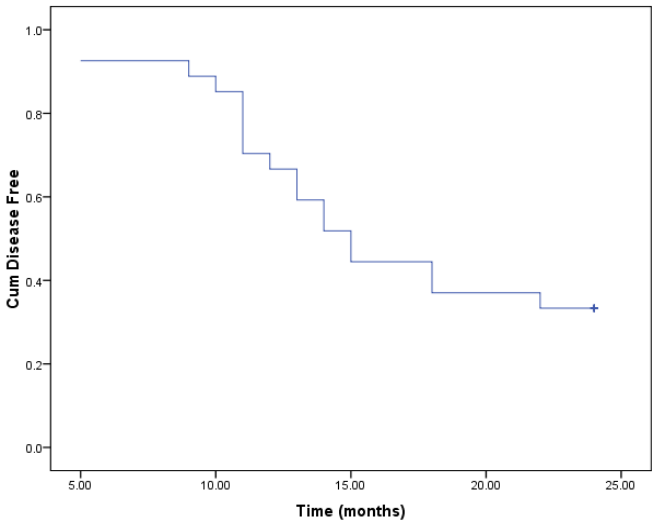

Figure ١: Disease free survival

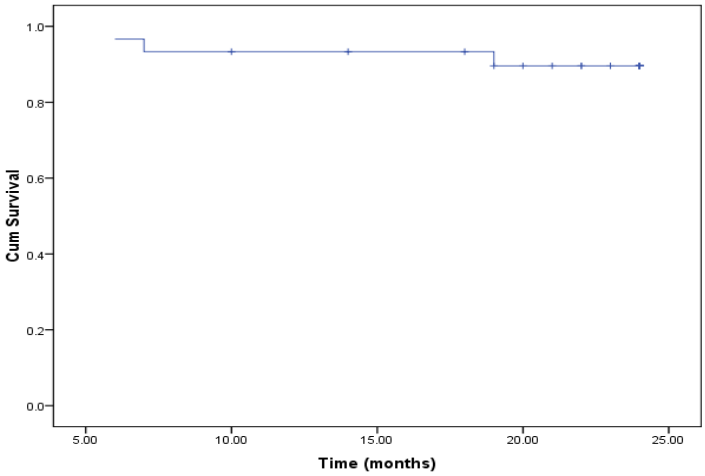

Figure ٢: Overall survival

Discussion

Although the collective data are strong in establishing the superiority of the combination of radiation with concurrent chemotherapy relative to standard radiation fractionation alone in the management of locally advanced head and neck cancer, there is variability of clinical trials in patient selection and regimens, leading to continuing debate as to which combined regimen should be considered standard**.** Furthermore, many questions remain to be answered, including whether the cisplatin dose can be altered to reduce acute and late toxicities without diminishing efficacy and whether neoadjuvant or adjuvant chemotherapy further improves the outcome of concurrent radiation and chemotherapy . [٧]

The randomized trial coordinated by the Swiss group for clinical cancer research. [٨] It was designed to address one of these questions, the total cisplatin dose was reduced (i.e. from the usual three to two cycles) and this approach seems to reduce the severity of systemic toxicity and mucositis without diminishing the impact on locoregional control and potentially on occult metastasis. This finding is consistent with the data of a phase III trial in nasopharyngeal carcinoma from the National Cancer Center of Singapore. The data from these two trials along with the observation form other studies showed that a substantial fraction of patients could not receive the third planned cisplatin dose of ١٠٠mg /m^{٢}, suggesting that a cumulative cisplatin dose of approximately ٢٠٠mg/m^{٢}, independent of the schedule, might be sufficient to yield a beneficial anti tumor effect**.** [٩]

Although much has been achieved in the way of improving DFS and OS by administering chemotherapy concurrently with RT, more is to be desired, especially concerning reduction of distant failure if adjuvant chemotherapy will be added. Different scheduling of adjuvant chemotherapy seems to have an additive effect.[٤,١٠,٥,٦]. These chemoradiotherapy trials included trials of induction chemotherapy followed by radiotherapy[٢,١١-١٣,٢٣], concomitant chemoradiotherapy[٢,١٤-١٧,١٩]), and adjuvant chemotherapy following definitive radiotherapy and/or surgery[٢,١٣,١٨]**.** A recent meta-analysis by Pignon and colleagues of chemoradiotherapy vs radiotherapy alone, first presented in ٢٠٠٠ and updated in ٢٠٠٩, included an additional ٢٤ trials that were comparisons of induction, concurrent, or adjuvant chemoradiotherapy. The meta-analysis found that there was a benefit of locoregional control for concurrent chemoradiotherapy compared with induction chemotherapy followed by radiotherapy.[٢,١٣]

In the present study, the median age of our patients was ٥٥.٥ years (range ٢٢-٦٦ years) with male to female ratio of ٢.٣: ١,compared to a study by Omar et al.,[٢٠] which showed that median age was ٤٤ years (range ١٨-٧٣ years) with male to female ratio of ٢.٣:١. And approximately the same finding in other western studies Al-Sarraf et al.,[١٠] and Wee et al.,,[٩] compared to a study by S. Abdelwahab et al.,[٢١], which showed that median age was ٥٩ years (range ٣٤-٧٨ years).Compared to a study by Semrau et al.,[٢٢], which showed that median age was ٥٥.٦ years (range ٣٤-٧٦ years).

We reported in the current study that larynx was the most common primary tumor site in ١٤ patients (٤٧٪) followed by nasopharynx which occurred in ٦ patients (٢٠٪), compared to Omar et al.,[٢٠] study which showed that nasopharynx was the most common occurred in ٢٣ patients (٦٤٪) followed by larynx in ٥ patients (١٤٪),compared to a study conducted by Agarwala and co-worker[٢٤], which showed that oropharynx was the first occurred in ٢٧٪.

The present study showed that ١٩ patients (٦٣٪) had stage III and ١١ patients had stage IV (٣٧٪), compared to S. Abdelwahab et al.,[٢١] study which showed that ١٣ patients (٢٨٪) had stage III and ٣٣ patients (٧٢٪) had stage IV. Also a study done by Chougule and his colleagues [٢٥] show that (٢٨٪) had stage III and ٣٣ patients (٧٢٪) had stage IV.

Fifty percent of our patient had treatment deviation during the concurrent CRT component. In Joseph et al.,, this figure was ٤١٪ , also ٨٠٪ of our patient completed the planned radiation dose comparing to that reported by Adelstin et al.,[٢٧], who reported ٨٤٪, in Omar et al.,[٢٠] study It was ٢٥٪ deviation and ٩٢٪ complete the planned radiation dose .

٧٠٪ of our patients completed the ٣ cycles of adjuvant chemotherapy as planned versus ٥٧٪ in Joesph et al.,[٥]

Regarding the toxicity profile in the current study, G-III –IV mucositis was the commonest side effect during the concurrent CRT phase (٣٠٪) this incidence was similar to Agarwala et al.,[٢٤] but lower than that reported by Hadir et al.,[٢٦] (٤٨٪), and other western studies where this incidence varied from ٤٠٪ to ٤٨٪ in Adelstein[٢٧] and Joseph.[٥] While Chougule et al.,[٢٥] reported a significant higher toxicities in ٩٠٪ of the enrolled patients.

Our present study showed that ORR was ٨٦.٧٪ where ١٤ patients (٤٦.٤٪) had a CR, ١٢ patients (٤٠٪) had a PR, ٢patients (٦.٧٪) had SD, ٢patients (٦.٧٪) had PD. These finding are similar to S. Abdelwahab et al.,[٢١] who reported that ORR was ٨٧٪,٢٨ out of٤٦ patients (٦١٪) enrolled in their study had attained CR, ١٢(٢٦٪) patients had PR,٢ patients (٤٪) had SD,٤ patients (٩٪) had PD. But our finding is better than that reported by Agarwala et al.,[٢٤] who reported that ORR was ٨٠٪, ٢٦ out of ٥٠(٥٢٪) patients enrolled in this study had attained CR, ١٤(٢٨٪) patients had PR, ٣(٦٪) patients had SD and ٧(١٤٪) patients had PD. While Chougule and his co-worker[٢٥] had reported more encouraging results than our finding; where they showed that ORR was٩١٪, ٦٥٪ of the ٤٣ patients had a CR, ٢٦٪had PR and ٤٪had PD. In Omar et al.,[٢٠] ٩٤.٤٪ enter in CR, and in Joseph et al [٥] who reported CR of ٨٦٪ at the end of both phases of treatment, however this incidence is lower than that achieved by Hadir et al.,[٢٦] who achieved ١٠٠٪ CR this may be explained by the nature of the disease itself, as this study was concerning of nasopharyngeal carcinoma patients only, however our study include nasopharyngeal carcinoma patients and other sites of the head & neck cancers.

Regarding the survival data in the current study, with a median follow up time of ٢٦ months for surviving patients range: (١٠-٤١ months).we reported that the median disease free survival (DFS) was ١٥ months (٩٥٪ CI: ١٢.٤-١٧.٥). And the estimated ٢ year DFS was ٣٣.٣٪. The median overall survival (OAS) was ٢١ months (٩٥٪ CI: ١٩-٢٣.٥) and the estimated ٢ years OAS was ٨٩.٦٪, While S. Abdelwahab et al.,[٢١] reported that with a median follow up time of ٢٩ months range: (٥-٣٧ months). The median DFS was ١٤.٥ months (٩٥٪ CI: ٩.٥-١٧months). And the estimated ٢ year DFS was ٣٦٪. The median overall survival (OAS) was ٢٤ months (٩٥٪ CI: ١٨-٢٩) and the estimated ٢ years OAS was ٤٢٪. In Agarwala et al.,[٢٤] study we see that after a median follow up time of ٦٩ months. The median DFS was ١٦ months (٩٥٪ CI: ٧-٢٤) and the ٣ year DFS was ٣٦٪. The median overall survival (OAS) was ٣١ months (٩٥٪ CI: ١٥-٤٤) and the estimated ٣ years OAS was ٤٥٪. Semrau et al.,[٢٢] reported that the ٢ years DFS ٤١٪ and that ٢ year OS was ٤٦.٣٪,while Omar et al.,[٢٠] reported that estimated ٢ year DFS and OS were ٧٨٪ and ٨٩٪ respectively. Joseph et al.,[٥] study repoted that the ٢ years DFS was ٧٧٪ and that ٢ year OS was ٨٨٪. Our finding is lower than that reported in Hadir et al.,[٢٦] study used concomitant chemoradiotherapy and adjuvant chemotherapy for treatment of nasopharangeal tumors only who reported DFS (٨١٪) and OS ٩٠٪. We compare our results with that reported by Brockstein et al.,[٢٨] who used concurrent CRT alone which was (٦٩٪) for the ٢ years DFS and ٧١٪ for ٢ years OS that is lower than OS we reported.

Conclusion

Concurrent chemoradiotherapy has produced improved results in patients with advanced head and neck cancers concerning locoregional control, disease free survival and overall survival more than radiotherapy alone , however more was achieved, especially concerning reduction of distant failure by addition of adjuvant chemotherapy. Cisplatin alone is lower than the combination with taxane in the response rate and disease free survival but the same in overall survival, however we could not ignore the occurrence of some side effects such as mucosits and neutropenia that lead to treatment gap during radiotherapy and delay of some chemotherapy cycles

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