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A Randomized Trial of Concurrent Chemoradiotherapy versus Radiotherapy in Advanced Carcinoma of the Uterine Cervix

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The purpose of our study was to determine whether the chemoradiation is better than radiotherapy alone with respect to survival and treatment toxicity in patients with advanced carcinoma of the cervix. From October 1990 to April 1995, a total of 122 patients with advanced cervical carcinoma were included in this study and randomly assigned to either radiotherapy or concurrent chemotherapy and radiotherapy. The patients in the concurrent group received cisplatin, vincristine, and bleomycin every 3 weeks for a total of four courses, in combination with radiotherapy concurrently. Sixty patients were randomized to the concurrent chemoradiotherapy, and 62 were randomized to the radiotherapy alone. A tumor response was observed in 88.3% of the patients in concurrent group and in 74.2% of the patients in radiotherapy group (P = 0.04). After a median follow-up of 46.8 months, the overall disease-free survival and actuarial survival rate at 3 years were 51.7 and 61.7% in the concurrent group, and 53.2 and 64.5% in the radiotherapy group, respectively. Treatment-related toxicity appears to be higher with the combination of radiotherapy and chemotherapy compared with radiotherapy alone (36.7% versus 17.7%, P = 0.02). However, analysis by Kaplan–Meier method showed that the actuarial survival was not statistically different between the chemoradiotherapy and radiotherapy groups (mean survival time: 38.1 months versus 41.5 months, P = 0.27). In conclusion, this study showed that concurrent multiagent chemoradiotherapy did not prove to be a superior definitive therapy over radiotherapy alone for patients with advanced cervical carcinoma.

INTRODUCTION

Over the past several decades, the prognosis of patients with locally advanced carcinoma of the cervix has been poor, particularly for those with bulky local tumors and extensive parametrial extension [1, 2]. The treatment of choice for advanced cervical carcinoma has traditionally been radiotherapy alone [1, 3]. The incidence of failure to control pelvic disease following radical irradiation is about 40%. This is associated with a high incidence of distant metastasis, in which 30% of patients subsequently developed metastases either alone or in combination with pelvic failure [3–5]. While no therapy has been proven more effective than radical external-beam plus intracavitary radiotherapy, considerable research effort, including addition of chemotherapy plus radiation, is currently being put into improving survival rate in patients with advanced carcinoma of the cervix. The rationale for adding chemotherapy to pelvic radiation is to provide systemic cytotoxic agents active against cervical cancer with the potential to enhance the radiosensitivity, to enhance local tumor control, and to eradicate micrometastasis.

Recently, a variety of studies have investigated how chemotherapy may be integrated into the management of patients with advanced cervical cancer. The use of concurrent chemoradiotherapy has shown promising therapeutic results in a variety of tumors [6–8]. The concurrent use of radiation and chemotherapy, either as a single agent or in combination, has also been demonstrated to be effective in the local control of advanced carcinoma of the cervix with acceptable toxicity as presented by several reports [9–16], and was also supported by our previous phase I and II trial [17]. However, most series were nonrandomized and failed to achieve an improvement in long-term survival. Therefore, to further test the hypothesis, a definitive statement about the optimal management in this situation required a prospective, randomized trial. Thus, we designed the randomized trial to compare the tumor response and survival rate of patients with advanced cervical carcinoma receiving concurrent chemotherapy and radiotherapy versus patients receiving radiotherapy alone.

The purpose of this randomized trial was to assess whether the chemoradiation is better than radiotherapy alone for locally advanced cervical carcinoma. We also compared the toxicity of the two compared groups after planned treatment.

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MATERIALS AND METHODS

Trial Design

This study was designed as a randomized, phase III trial conducted at the Chang Gung Memorial Hospital in Taiwan. From October 1990 to April 1995, patients with advanced carcinoma of the uterine cervix were entered on the study and randomly assigned to either radiotherapy or concurrent chemoradiotherapy. Before randomization, patients were stratified by stage (stage IIb bulky versus stage IIIB). The trial compared the efficacy and tolerability of concurrent chemotherapy and radiotherapy versus radiotherapy alone for the treatment of patients with advanced cervical cancer.

Patients

A total of 122 patients with advanced carcinoma of the uterine cervix were included in this study. Patients with previously untreated stage IIb bulky or stage IIIb advanced cervical carcinoma were eligible for study. Other eligibility criteria consisted of a pathologically verified squamous cell carcinoma of the cervix, a Karnofsky performance status index of 80% or above, and an age of younger than 70 years. Patients with stage IIB tumors had to have bulky tumors larger than 4 cm and extensive parametrial invasion. The patients could have no history of previous malignancy, chemotherapy, or radiotherapy. Adequate hepatic, renal, and cardiopulmonary functions were essential. Informed consents were obtained from all patients, and the study protocol was approved by the Protocol Committee of Chang Gung Memorial Hospital.

The disease was staged according to the International Federation of Gynecology and Obstetrics (FIGO) in 1991. Pretreatment evaluation included a complete medical history and physical examination, complete blood count, serum electrolytes, chemistry profile, tumor markers, chest X ray, an electrocardiogram, and contrast-enhanced computerized tomography (CT) of the abdomen and pelvis. All patients had protoscopy, cystoscopy, bone scan, and biopsy of any suspected lesions. Patients with radiographically suspicious paraaortic lymph nodes underwent a CT-guided percutaneous needle aspiration of the node. Extraperitoneal staging laparotomy was performed if aspiration cytology was negative. Any enlarged or suspicious nodes were excised and sent for histopathologic interpretation. Patients with documented disease beyond the pelvis were excluded, as were patients with positive paraaortic lymph nodes.

Treatment Plan

Eligible patients were randomized to receive concurrent chemoradiotherapy or radiation therapy alone. In the radiation group, patients received external beam X-ray treatment followed by intracavitary brachytherapy. External beam irradiation was started on Day 1 and delivered using a linear accelerator of 10-MV photons to the whole pelvis using a four-field box technique. A dose of 4400 cGy was delivered in 22 equal fractions over 30 to 35 days. This was followed by six courses of intracavitary brachytherapy 1 to 2 weeks after external beam radiotherapy was completed. Treatment was given using a remote-control afterloading system to give 430 cGy at point A in each intracavitary brachytherapy, as described previously [18]. In the concurrent chemoradiotherapy group, chemotherapeutic regimens consisted of cisplatin (50 mg/m^2 body-surface area intravenously at the rate of 1 mg/min on Day 1), vincristine (1 mg/m^2 intravenously push on Day 2), and bleomycin (25 mg/m^2 body-surface area intravenously infusion in divided doses on Days 2, 3, and 4) which were given starting on Day 1 of radiotherapy and then every 3 weeks for a total of four courses. Antiemetic treatment was given before and after cisplatinum-based chemotherapy. Flexible granulocyte colony-stimulating factor (G-CSF) 2 μg/kg/day administration was used to prevent neutropenia and further infection. The patients had to have a white-cell count of at least 3000/m^3 and a platelet count of at least 100,000/m^3 before the next course could be administered. Chemotherapy was to be delayed week by week until the neutrophil count recovered to $>1500/\mu$l, platelet count recovered to $>100{,}000/\mu$l. Cisplatin was to be delayed if serum creatinine levels did not return to 1.5 mg/dl, and creatinine clearance to 60 ml/min. If this delay exceeded 3 weeks, the patient was withdrawn from the study.

The local response to treatment was evaluated at 1 month after completion of therapy by physical examination and abdominopelvic computerized tomography. Tumor response definitions used were based on World Health Organization (WHO) criteria [19]. All adverse effects and laboratory abnormalities for chemotherapy were graded according to the toxicity criteria of the Gynecologic Oncology Group [20]. Toxicity of chemotherapy was assessed before each course.

Study End Point

The primary objectives were to compare the two treatment groups with respect to tumor response, failure patterns, disease-free interval, and actuarial survival. The secondary objectives were to compare the two treatment groups with respect to treatment-related toxicities, treatment delays, and completeness. Survival was defined as the observed length of life from protocol entry to death or until January 5, 1997 when the data analysis was finished and patients were still alive. Disease-relapsed interval was defined as the time from entry to local recurrence or distant metastasis.

Statistical Considerations

In the study design, it was assumed that 60 eligible patients would be randomly assigned to each treatment group. At a two-sided P value of 0.05, with the use of a Pearson χ^2 approximation, the estimated power was 80% to detect

TABLE 1
Patient Characteristics According to Treatment Group

Characteristics	Concurrent CT and RT (n = 60)	Radiotherapy (n = 62)
Age		
<50	16	20
>50	44	42
Stage		
IIb bulky	28	30
IIIb	32	32
Parametrial involvement		
Unilateral	28	32
Bilateral	32	30
Grade		
I	13	11
II	20	21
III	27	30
Hydronephrosis		
Yes	11	9
No	49	53
Staging laparotomy	3	4

an improvement of 25% in survival with the concurrent therapy at the $\alpha = 0.05$ level (two-sided test). The actuarial disease-free survival and overall survival of patients with complete follow-up were estimated by the life-table method of Kaplan and Meier. Differences in survival rates were assessed by the log-rank test. Comparisons of variables between groups were based on the χ^2 test. All eligible patients were included in the analysis regardless of whether they completed the assigned treatment.

RESULTS

The study began in October 1990 and ended in April 1995. A total of 122 patients with advanced carcinoma of the uterine cervix were entered and all were eligible for follow-up evaluation. Among them, 60 patients were randomized to the concurrent chemotherapy and radiotherapy, 62 were randomized to the radiotherapy alone. The median follow-up was 46.8 months (range, 12–69 months). The mean age of the patients was 56.2 years (range, 33–68 years) in the concurrent group, and 58.7 years (range, 41–69 years) in the radiotherapy group. Patient characteristics were well balanced between the compared groups. Detailed data of the presenting patient characteristics with age, FIGO stage, tumor size, histologic grade, and parametrium status were listed in Table 1.

Of the chemoradiotherapy group, 43 patients completed four courses of chemotherapy, 11 patients received three courses, and 6 patients received two courses of chemotherapy. Among them, interrupted radiotherapy with delayed treatment because of treatment-related toxicity was observed in 9 cases. A review of the reasons for these unscheduled interruptions of therapy revealed that 8 were due to hematological toxicity, and 1 was due to elevated GOT and GPT. The duration of the unplanned interruption was 1 week in 5 and 2 weeks in 2, and 2 patients were unable to complete the planned radiotherapy. Of the radiotherapy group, 60 patients completed radiotherapy with no delays of treatment for toxicity, whereas the planned radiotherapy was interrupted for 1 week in 2 patients because of radiation protitis or neutropenia. The duration of therapy for the patients was 59 days (range, 49–78 days) versus 51 days (range, 47–65 days) in the chemoradiotherapy and radiotherapy groups, respectively. The incidence of delayed treatment was significantly higher in patients with concurrent chemoradiotherapy than those patients with radiation alone (15.0% versus 3.2%, $P = 0.02$). However, there was no difference in completeness between concurrent group and radiotherapy group (96.7% versus 100%, $P = 0.24$).

Tumor Response

Table 2 shows the tumor response for the two groups. A tumor response was observed in 88.4% (53/60) of the patients in concurrent group and in 74.2% (46/62) of the patients in radiotherapy group. The tumor response was significantly higher in patients receiving concurrent chemoradiation than in patients who received radiation alone ($P = 0.04$).

Toxicity

Acute (between initiation of therapy to 6 weeks after therapy) and late treatment-related toxicity (6 weeks after therapy) are listed in Tables 3 and 4. The acute treatment-related toxicity (grade 3 or 4) appears to be higher with the concurrent chemoradiotherapy group when compared with radiation group (36.7% versus 17.7%, $P = 0.02$). Although there was no significant difference between the two compared groups with regard to treatment-related late toxicity (concurrent group 23.3% versus radiation group 12.9%; $P = 0.13$),

TABLE 2
Comparison of Tumor Response between the Two Compared Groups

	Concurrent CT and RT (n = 60)		Radiotherapy (n = 62)	
Response	n	%	n	%
CR	46	76.7	38	61.3
PR	7	11.7	8	12.9
SD	6	10.0	14	22.6
PD	1	1.7	2	3.2

Note. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

TABLE 3
Treatment-Related Acute Toxicity (Grade 3 or 4)

	Concurrent CT and RT (n = 60)		Radiotherapy (n = 62)	
Toxicities	n	%	n	%
Nausea/vomiting	9	15	5	8.1
Diarrhea	6	10	10	16.1
Leukopenia	11	18.3	8	6.5
Thrombocytopenia	4	6.7	2	3.2
Anemia	14	23.3	5	8.1
Nephrotoxicity	5	8.3	0	0
Total	22	36.7	11	17.7

Note. There were 9 patients requiring treatment delays because of treatment-related toxicity during chemoradiotherapy. Two patients were unable to complete the planned chemoradiotherapy because of treatment-related neutropenia.

a nonsignificant trend toward a higher rate of late toxicity in the chemoradiotherapy group is evident.

All these acute toxicities were successfully treated with conservative management, except one death related to neutropenic sepsis after chemoradiotherapy. Additionally, there was one death related to late toxicity due to a small bowel obstruction with perforation and following with sepsis after chemoradiotherapy. No treatment-related deaths occurred in the radiotherapy group.

Failure Patterns

The failure patterns were evaluated and listed in Table 5. An analysis of the patterns of failure reveals that the incidence of pelvic failure was equally distributed between the treatment groups (31.7% versus 30.6%, $P = 0.93$). Additionally, there was also no difference in the incidence of distant failure between the chemoradiotherapy group and the radiotherapy group (21.6% versus 29%, $P = 0.47$). The median time to pelvic recurrence was 15 months (range, 7–19 months), whereas the median time to distant recurrence was 21 months (range, 12–33 months).

TABLE 4
Treatment-Related Late Toxicity

	Concurrent CT and RT (n = 60)		Radiotherapy (n = 62)	
Complications	n	%	n	%
Radiation protitis	6	10	4	6.5
Radiation cystitis	3	3.3	2	3.2
Intestnial obstruction	2	3.3	0	0
Fistula	3	5	2	3.2
Total	14	23.3	8	12.9

TABLE 5
Patterns of Failure

	Concurrent CT and RT (n = 60)		Radiotherapy (n = 62)	
Sites of failure	n	%	n	%
Central	14	23.3	11	17.7
Central + distance	5	8.3	8	12.9
Distance	8	13.3	10	16.1

Survival and Disease-Free Survival

Of the chemoradiotherapy group, 31 patients (51.7%) are alive without evidence of disease, 6 (10%) remain alive with disease, and 21 (35%) died of disease at 7–48 months. Regarding patients with treatment incompleteness, those two patients who did not complete their planned treatment course because of treatment-related toxicity were dead of disease at 13 and 16 months. Of the 9 patients requiring treatment delays, 7 patients (77.8%) died of disease (5) or are alive with disease (2), whereas 18 of the 49 patients (36.7%) who had completed their planned treatment without treatment delays died of disease or are alive with disease. Of the radiation group, 33 patients (53.2%) are alive without evidence of disease, 7 (11.3%) remain alive with disease, and 22 (35.5%) died of disease at 12–45 months. After a median follow-up of 46.8 months, the disease-free survival and actuarial survival rates at 3 years for patients in the concurrent chemoradiotherapy group were not statistically different compared with patients in the radiotherapy group (51.7% versus 53.2%, $P = 0.92$; and 61.7% versus 64.5%, $P = 0.88$, respectively). Figures 1 and 2 show the 3-year disease-free and overall

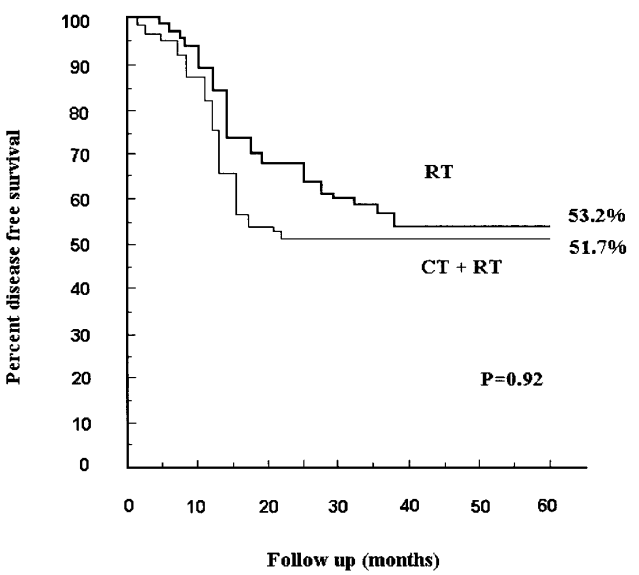

FIG. 1. Overall disease-free survival measured from randomization.

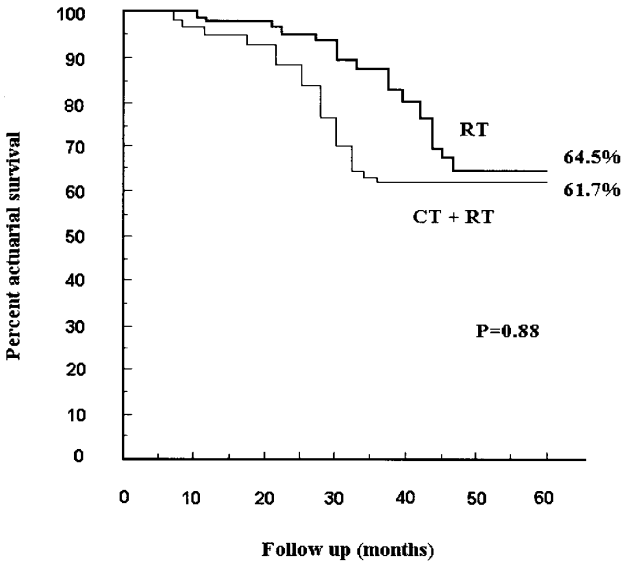

FIG. 2. Actuarial survival measured from randomization.

survival curves for the two groups. Analysis by Kaplan–Meier method showed that the actuarial survival was not statistically different between the chemoradiotherapy and radiotherapy groups (mean survival time: 38.1 months versus 41.5 months, $P = 0.27$).

DISCUSSION

Treatment results using radiation alone in women with locally advanced cervical cancer are unsatisfactory. These failures may be attributed to large central tumor volumes, parametrial extensions of disease resistant to local therapies, or metastatic disease outside the radiation field. Several studies have confirmed that bulky cervical cancer and extensive parametrial invasion are indeed poor prognostic features [1, 2]. Radiation effects are dependent on well-oxygenated tumor cells [21]. In theory, bulky tumors have significant hypoxic cell populations that are relatively radioresistant [22]. The problem of enhanced pelvic control cannot be approached simply by increasing radiation doses because of the additional complications produced by conventional radiation. Thus, advanced carcinoma, such as those observed in our study, having a large hypoxic cell component, may be ineffective if receiving radiotherapy alone. Therefore, the design of a more efficient treatment modality, such as the addition of chemotherapy plus radiotherapy, with the objective of increasing tumor control and long-term survival for patients with advanced cervical carcinoma, is advocated.

To date, cisplatin is one of the most active drugs tested in this tumor [23, 24]. Cisplatin has been the mainstay of treatment for cervical cancer, consistently showing a 20–25% response rate [25, 26]. This drug has also been shown to be a radiosensitizer *in vitro* and *in vivo* with documented activity in squamous cell carcinoma [27, 28]. Moreover, cisplatin combined with vincristine and bleomycin has become more popular, and has been reported to be active in cervical cancer [29, 30]. Therefore, in an attempt to improve tumor control and survival in patients with advanced cervical carcinoma, the treatment efficacy and tolerability of combined radiotherapy and chemotherapy using cisplatin-based chemotherapy for the treatment of patients with advanced cervical cancer needs to be explored.

Over the past few years, there have been multiple studies published which have retrospectively analyzed the outcome of patients with advanced cervical carcinoma who received concurrent radiotherapy and chemotherapy [9–16]. The concept of concurrent chemoradiotherapy offers a number of theoretical advantages, which produces no delay in the start of definitive radiotherapy, no time gap to induce cross-resistance, and the possibility of eradication of subclinical metastasis. In addition, the possibility of synergistic action between radiation and chemotherapy may lead to increased tumor cell kill [27, 28]. The published trials in advanced cervical carcinoma with concurrent chemoradiotherapy, either a single-agent weekly cisplatin [13–16] or in combination with cisplatin–5-FU or cisplatin–bleomycin–vincristine [9–12, 17], yield tumor response rates of approximately 80%, and 3-year survival rates reached 50 to 60% of patients. However, most of these results were nonrandomized and were based on a small sample size. Only a randomized trial, using a single agent of weekly cisplatin in combination with radiotherapy, has shown a significant improvement in local–regional control when compared with radiation alone [15]. A later report of this group confirmed that the addition of cisplatin plus radiotherapy failed to show any significant improvement in long-term survival [16]. Therefore, to test the hypothesis of concurrent chemoradiotherapy improving the survival rate of advanced cervical cancer, in 1990 we began a phase III randomized trial comparing concurrent chemoradiotherapy versus pelvic radiation alone in patients with advanced cervical carcinoma at our institution. To further increase the systemic activity and the radiation-enhancing potential of the chemotherapy, we chose cisplatin-based regimens with vincristine and bleomycin in this trial because it had proven high efficacy of local control in our previous phase I and II trials for patients with advanced cervical carcinoma [17].

Although the response rate of 88.4%, following concurrent chemoradiotherapy, in our study is very encouraging when compared with 74.3% of the radiotherapy group at the end of therapy, this study does not provide evidence that chemoradiation is better than radiotherapy alone with respect to survival. Our results indicated that, despite the excellent early tumor response seen during treatment, the benefit of concurrent chemoradiation in terms of reduced mortality and increased pelvic control rates may not be as great as that suggested by other reports. Our study also revealed that the

patterns of recurrences were not changed by the concomitant therapy with chemotherapy and radiotherapy. The pelvis is still the predominant site of failure in around 30%. However, a high proportion of patients who failed in this trial had a component of distant failure. Computerized tomography lacks sensitivity for identifying micrometastasis outside the pelvic radiation therapy field. This finding has been associated with occult extrapelvic disease [31]. There appears to be a small decrease in distant relapse among the concurrent chemoradiation group, although the difference was not significant.

The most likely explanation for the poor results in the concurrent chemoradiotherapy group is the higher treatment-related toxicity, and that could limit the dose of definitive radiation employed or interrupt the planned radiotherapy. An equally likely explanation is the negative impact of prolonged treatment time caused by toxicity-induced delays. Indeed, in our trial, the treatment-related toxicity was severe and resulted in delayed radiotherapy in 15% of patients after chemoradiotherapy, in which 77.8% of patients with treatment delays recurred or died of disease. Additionally, the two patients who did not complete their planned treatment course died of disease. The incidence of acute and late complications encountered in our series was higher than anticipated. In our trial, grade 3 or 4 treatment-related toxicities were observed more often on chemoradiotherapy than radiotherapy alone. Moreover, two patients died of septicemia following chemoradiotherapy. Our results demonstrated that multiagent chemoradiotherapy, concurrently administrated with radiation to improve tumor response, can also produce serious acute and late toxicities, and life-threatening complications.

On the other hand, a probable explanation for the poor survival in advanced cervical cancer patients, in spite of a satisfactory rate of initial response, may be the enhancement of accelerated tumor proliferation during treatment. Some authors have reported that clonogen repopulation in squamous cell carcinoma of the head and neck region accelerates after radiotherapy [32]. Chemotherapy could also lead to an accelerated regrowth of surviving clonogens. The accelerated repopulation in the treatment may involve only a small number of surviving cells, which could be omitted by post-treatment investigations. Thus, tumor masses would be still regressing while the subclinical clonogenic cell repopulation in accelerating. Therefore, in patients with locally advanced carcinoma of the cervix, improvement in local control will not translate into an improved long-term outcome because this gain will be offset by the eventual development of a relapse.

In conclusion, when comparing patients with concurrent therapy of radiotherapy and chemotherapy to radiotherapy alone, our study showed that concurrent multiagent chemoradiotherapy did not prove to be a superior definitive therapy for patients with advanced cervical carcinoma. It may be that the multiagent chemotherapy with these drugs, dose, and schedule used in this study is too toxic to use with concomitant radiation therapy. It is desirable for future studies to see whether other chemotherapeutic regiments such as 5-FU or weekly cisplatin would be more likely to be tolerable and be associated with fewer treatment interruptions. Such trials are currently underway.

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