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ORIGINAL ARTICLE

The impact of dietary regimen compliance on outcomes for HNSCC patients treated with radiation therapy

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Abstract

Objective To analyze nutritional factors and compliance with dietary recommendations for associations with overall survival (OS) and progression-free survival (PFS) in patients receiving definitive RT for laryngeal and oropharyngeal cancers.

Materials/methods We identified 352 patients with non-metastatic laryngeal (146) and oropharyngeal (206) cancer treated with definitive RT between 2004 and 2013. Disease and patient characteristics, treatment information, sarcopenia based on muscle areas at L3 level on CT, compliance with the nutritional program, and clinical outcomes data were tabulated. Descriptive statistics, Kaplan-Meier survival analysis, and log rank tests were performed, and Cox regression models were used to examine predictors of OS and PFS.

Results The median follow-up for the entire cohort was 22.86 months. The actuarial rates for OS were 91, 86, and 73% at years 1, 2, and 5, respectively. Of patients with abdominal CT prior to starting RT, 70.9% (112/158) were sarcopenic with a median muscle mass index of 48.2 (range 30.4–70.9) for males and 35.9 (range 24.6–53.2) for females. The majority (85.8%) of patients met with a dietitian during their course of RT and 62.6% of these patients were compliant with the nutritional program. Compliance with the nutritional program resulted in 27% (HR 0.73, 95% CI 0.43–1.26) protection from death (did not reach significance) and 31% (HR 0.69, 95% CI 0.50–0.94) significant protection from disease progression. Higher pretreatment BMI was associated with a lower risk of death (HR 0.94, 95% CI 0.90–0.99) and disease progression (HR 0.96, 95% CI 0.93–0.99).

Conclusion Laryngeal and oropharyngeal cancer patients treated with definitive RT who are compliant with regular dietetic counseling and contact appear to have improved outcomes.

Trial registration Not applicable

Keywords Nutrition · Compliance · Radiation therapy · Head and neck cancer

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Background

Worldwide, there are over 500,000 new head and neck cancer cases diagnosed annually [1]. Approximately 62,000 new head and neck cancer diagnoses and 13,000 deaths per year occur in the USA alone [2]. Malnutrition is a common comorbid condition for head and neck cancer patients. Thirty-five to sixty percent of head and neck cancer patients present as malnourished at the time of diagnosis with greater than 10% unintentional weight loss of usual body weight [3]. A large tumor burden can cause trismus, dysphagia, and odynophagia that can increase the risk of aspiration or obstruction of the aerodigestive tract [3]. Long-term poor nutritional intake, which may be related to excessive alcohol and tobacco use, also contributes to suboptimal nutritional status before treatment begins [4]. Furthermore, metabolic derangements associated with the cancer itself, including early stages of cancer cachexia, may also impact nutritional status pretreatment [5].

Many head and neck cancer patients experience weight loss, gastrointestinal distress, anorexia, fatigue, and sarcopenia (loss of lean body mass) before, during, and after treatment. This further impacts nutritional intake and functional status. Sarcopenia in cancer patients is associated with poorer outcomes and decreased tolerance of cancer therapy in multiple malignancies [6].

Head and neck cancer patients can be treated with surgery, chemotherapy, and radiation therapy (RT). The adverse effects of these treatment modalities can exacerbate impaired nutritional statuses of head and neck cancer patients [7]. Radiation therapy is an effective modality for obtaining locoregional control of solid tumors, but is also associated with many nutrition-related toxicities for head and neck cancer patients. Combining treatment modalities augments nutrition-related adverse effects, placing head and neck cancer patients at even higher nutritional risk [7].

It is important to improve nutritional status in cancer patients, as malnourished patients are at an increased risk of delayed wound healing, impaired immune responses, medical complications, and mortality [8]. It is estimated that 20% of cancer patients die from complications associated with malnutrition rather than direct effects of the disease itself [9]. Deterioration of nutritional status may also result in treatment interruption and thus decrease the therapeutic effect of antineoplastic interventions [9]. Early nutrition interventions in head and neck cancer patients undergoing chemoradiotherapy result in improved treatment tolerance and fewer hospital admissions [10]. Nutritional interventions are also associated with an increased quality of life (QOL) post RT [11]. Typical nutrition interventions include individualized dietary counseling to increase protein, calorie, and nutrient density of intake, the use of oral nutrition supplements, enteral nutrition feeding tube placement, and parenteral nutrition interventions [12]. Pretreatment feeding tube placement is controversial due to risks of complications, effect on QOL, and long-term tube dependence. However, the placement of feeding tubes upon indication of need secondary to treatment toxicities may be necessary to prevent further deterioration of nutrition status during and after the treatment course [13]. Currently, sufficient evidence is lacking to develop a standardized enteral nutrition protocol in head and neck cancer patients [14].

At our institution, we initiated a nutritional program where patients treated with definitive RT are evaluated and closely followed by an oncology-registered dietitian. In this study, we examined the association of nutritional counseling and compliance with overall survival (OS) and progression-free survival (PFS) of patients receiving definitive RT for laryngeal and oropharyngeal cancers.

Material/methods

Study design

In this retrospective review, patients with head and neck cancer who were treated with definitive RT between 2004 and 2013 at a tertiary care teaching hospital were considered for the study. The cohort consisted of a total of 352 patients with non-metastatic oropharyngeal (206) and laryngeal (146) cancer.

Disease and patient characteristics, treatment information, and clinical outcomes data were tabulated. Weekly nutritional counseling by a registered dietitian was initiated for patients who were treated with definitive RT during their treatment course. A sample of the weekly nutritional assessment form is shown in supplementary figure 1. During these meetings, patients were provided education regarding calorie and protein density and strategies to maintain adequate caloric intake. They were recommended to increase the frequency of eating based on time and appetite. If patients were still unable to maintain their caloric intake, they were recommended commercial or homemade nutritional supplements of at least 1.5 kcal/ml. Patients were also encouraged to continue weekly follow-up with the registered dietitian. Adherence to the nutritional program was scored weekly and patients were deemed non-compliant with nutritional program if they canceled > 25% of their appointments with the dietitian, refused nutritional counseling, or did not follow recommendations as documented in dietitian's note.

Sarcopenia

Sarcopenia, or loss of skeletal muscle, has been associated with poor tolerance of cancer therapy [15, 16]. Of the 352 patients, 158 patients had a pretreatment CT including the abdomen within 30 days of RT start. These were used to estimate the prevalence of sarcopenia in this patient population.

Sarcopenia was defined based on muscle areas visualized on CT at the level of L3 using after correcting for body surface area (BSA) and gender using cutoffs established by Prado et al. [16, 17].

$$\text{Males}: \text{muscle area} \div \text{BSA} < 55\ \text{cm}^2/\text{m}^2$$
$$\text{Females}: \text{muscle area} \div \text{BSA} < 39\ \text{cm}^2/\text{m}^2$$

Outcome measures

Outcome measures in this study included overall survival and progression-free survival. Event times were calculated from the date of RT completion and patients were censored at the time of last follow-up.

Statistical analysis

Descriptive statistics were calculated, the continuous variables are presented as mean (sd) or median (range) and continuous variables were presented as frequency counts and percentages. The association of covariates by dietary compliance and death was examined using Student's *t* test or Mann-Whitney *U* test and chi-square test. The distribution of time to death and time to disease progression was estimated using the Kaplan-Meier procedure and the difference in distribution was examined using log rank tests. The risk factors for time to death and disease progression were analyzed using the Cox regression model. The covariates that were significant at 20% level of significance in the univariate Cox model were considered for the final model. The data were analyzed using SAS software version 9.4.

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Results

The median follow-up for the entire cohort was 22.86 (0.56–116) months. The actuarial rates for OS were 91, 86, and 73% at years 1, 2, and 5, respectively. Of the 352 patients included in the study, 85.8% (302/352) met with a dietitian during their RT treatment and 62.6% of patients who met with dietitian were compliant with the nutritional program. The distribution for reasons patients were scored non-compliant is shown in Fig. 1. The median time (interquartile range IQR) when patients became non-compliant was 4 weeks (IQR 3–5 weeks). The patient and clinical characteristics of study sample by dietary compliance are presented in Table 1. The majority of participants (81.1%) had a primary head and neck tumor of stage III or greater. Baseline BMI of study patients did not differ significantly between groups. Patients that were deemed non-compliant to nutritional interventions had significantly longer treatment durations with 26.5% of patients having

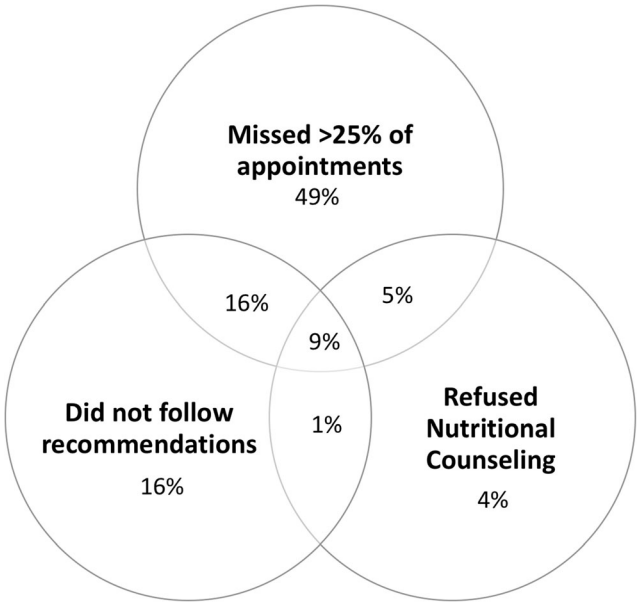

Fig. 1 Venn diagram for the reason patients were scored as non-compliant

Table 1 Patient and clinical characteristics of study sample by dietary compliance status

	Compliant with dietary regimen ($n = 189$) *N* (%)	Non-compliant with dietary regimen ($n = 113$) *N* (%)	*P* value
Median age (years)	61	61	0.49*
Smoking (> 10 pack years)	68.8%	84.1%	0.11
Alcohol (> 2/day)	32.8%	39.8%	0.47
Drug use	15.8%	22.1%	0.31
Charlson comorbidity score (median)	7 (3–21)	7 (2–17)	0.14*
Primary tumor			0.02
Oropharynx	56.6%	67.3%	
Larynx	43.3%	32.7%	
Stages III & IV (%)	75.7%	90.3%	0.12
Primary tumor volume (ml) (median)	12	12	0.97
PET total glycolytic activity (primary)	67	88	0.41
PET total glycolytic activity (primary+LN)	122	138	0.48
Systemic therapy	70.9	84.1	0.87
BMI (median)	26.0	25.5	0.718
Sarcopenic	64.7	76.6	0.12
Treatment time > 49 days	14.8	26.5	0.03

P values using χ^2 testing to compare compliant and non-compliant patients, except as indicated

*Mann-Whitney *U* test

treatment time > 49 days compared to 14.8% for compliant patients ($P = 0.03$). The median (IQR) treatment times for non-compliant and compliant patients with nutritional program were 49 days (IQR 46–55) and 49 days (IQR 45–52), respectively.

Nutrition

Multivariable Cox proportional hazards modeling for patients who met with dietitian after adjusting for demographic and clinical variables including tumor volume, Charlson comorbidity index, number of RT treatment days, and pretreatment BMI demonstrated that compliance with the nutritional program resulted in 27% (HR 0.73, 95% CI 0.43, 1.26) protection from death (Table 2), which did not reach statistical significance. Compliance also led to a 31% (HR 0.69, 95% CI 0.50, 0.94) protection in disease progression, which was significant (Table 3). The Kaplan-Meier curves can be seen in Figs. 2 and 3

Sarcopenia

Of patient with abdominal CT prior to starting RT, 70.9% (112/158) were sarcopenic with a median muscle mass index of 48.2 (range 30.4–70.9) for males and 35.9 (range 24.6–53.2) for females. Seventy-three percent of oropharynx patients compared to 68.8% of larynx patients were sarcopenic. Sarcopenia was not independently predictive for increased risk for overall death and disease progression. However, higher pretreatment BMI was associated with a significantly lower risk for death (HR 0.94, 95% CI 0.90, 0.99) and disease progression (HR 0.96, 95% CI 0.93, 0.99).

Discussion

It is well established in the literature that head and neck cancer patients are at an increased risk for malnutrition, which can directly impact treatment outcomes and quality of life [3]. This retrospective study bolsters evidence that deterioration of nutritional status during head and neck cancer treatment is a serious problem warranting early nutritional intervention by

Table 2 Cox regression model. Adjusted hazard ratio, 95% confidence interval, and *P* value for time to death (overall survival)

Variable	HR	95% CI		*P* value
Compliance with nutritional program	0.731	0.425	1.257	0.2572
Comorbidity score	1.168	1.121	1.217	< 0.0001
Treatment days	1.009	0.992	1.026	0.2834
Higher pretreatment BMI	0.941	0.895	0.990	0.0185

Table 3 Adjusted hazard ratio, 95% confidence interval, and *P* value for time to progression (PFS survival)

Variable	HR	95% CI		*P* value
Compliance with nutritional program	0.687	0.501	0.941	0.0194
Comorbidity score	1.208	1.132	1.290	< 0.0001
Treatment days	1.026	1.004	1.048	0.0183
Higher pretreatment BMI	0.959	0.931	0.988	0.0056

oncology-registered dietitians. We demonstrated that laryngeal and oropharyngeal cancer patients treated with definitive RT who are compliant with regular dietetic counseling and contact had a 27% protection from death, although this did not reach statistical significance, and 31% significant protection from disease progression.

Of interest, more oropharynx cancer patients and less larynx cancer patients (41.5 vs 31.1%, respectively) are in non-compliant with the dietary regimen group. One possibility for this is that patients with oropharynx primary have a larger portion of the pharyngeal and oral mucosa receiving higher doses of radiation thereby leading to worse side effects making it more difficult to comply. As some oropharynx patients are at higher risk for non-compliance, it may be helpful to allocate additional resources to these patients in order to improve compliance with dietary regimen such as providing nutritional education and counseling to foster more patient/caregiver-drive or use of home care.

There is no universally accepted definition of malnutrition, but the American Society for Parenteral and Enteral Nutrition (ASPEN) and the Academy of Nutrition and Dietetics (AND) recently established guidelines for defining malnutrition based

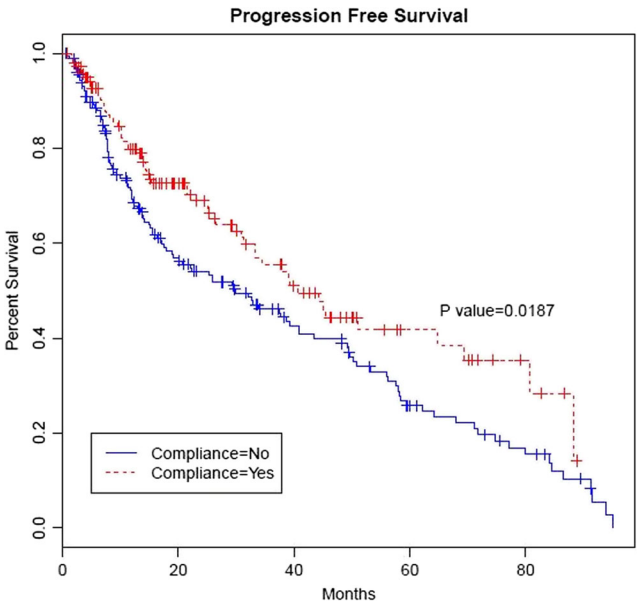

Fig. 2 Kaplan-Meier curves for progression-free survival for compliant and non-compliant patients

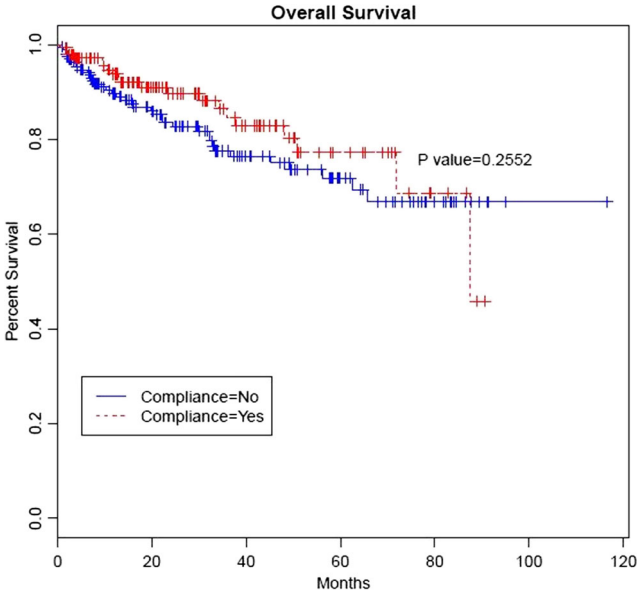

Fig. 3 Kaplan-Meier curves for overall survival for compliant and non-compliant patients

on a patient's degree of inflammation. The three main categories are described as (1) simple starvation, where inflammation is not present; (2) mild to moderate inflammation, which includes inflammation of chronic diseases, including cancer cachexia (a syndrome mediated by the acute phase response characterized by increased proteolysis, lipolysis, anorexia, and resting metabolic expenditure, coupled with impaired tissue anabolism) and sarcopenic obesity; and (3) severe inflammation, which may occur with trauma or sepsis. ASPEN and AND also describe six clinical parameters to diagnose malnutrition: (1) insufficient caloric intake, (2) loss of body weight, (3) loss of lean body mass, (4) subcutaneous fat loss, (5) fluid accumulation (localized or generalized), and (6) loss of functional status as measured by diminished handgrip strength [4]. Oncology-registered dietitians utilize these parameters in their comprehensive nutrition assessments to determine nutritional status and level of nutritional risk.

Head and neck cancer patients are treated with surgery, chemotherapy, and radiation therapy. The adverse effects of these treatment modalities often negatively impact nutritional statuses of head and neck cancer patients. Surgical interventions can cause dysphagia and odynophagia, impacting speech and swallowing. Systemic chemotherapy is also associated with nutrition-related toxicities, including nausea, vomiting, mucositis, anorexia, dysgeusia, myelosuppression, fatigue, constipation, diarrhea, and electrolyte abnormalities [7]. Radiation therapy, although effective in obtaining locoregional control of solid tumors and prolonging patient survival, is associated with many nutrition-related side effects for head and neck cancer patients as well. These include mucositis, xerostomia, dysgeusia/ageusia, decreased appetite, increased phlegm production, dysphagia, and odynophagia [18]. A prospective study by Unsal et al. found that 24% of head and neck cancer patients presented as malnourished pre-treatment and 88% of those patients were malnourished post radiation treatment [9].

For patients undergoing active anti-neoplastic therapy, the American Cancer Society outlines the following goals of nutritional care: prevent or resolve nutrient deficiencies, achieve or maintain a healthy weight, preserve lean body mass, minimize nutrition-related side effects, and maximize quality of life [19]. The Oncology Nutrition Dietetic Practice Group of the Academy of Nutrition and Dietetics recommends that the goal of nutritional care for head and neck cancer patients specifically should be to maintain weight during and after cancer treatment until the patient is able to consume solid food, successfully complete treatment and minimize breaks and/or dose reductions, minimize weight loss in overweight or obese patients until the patient is fully recovered from treatment, and maintain weight as patients transition from enteral nutrition to oral feedings [7]. Typical nutrition interventions by oncology-registered dietitians in the head and neck cancer population include personalized nutritional counseling, supplementation with oral nutrition beverages and modular products, enteral feeding tube placements, and less commonly, parenteral nutrition interventions [12]. The use of prophylactic feeding tube placements for head and neck cancer patients is controversial. While a prophylactic feeding tube can improve intake for patients unable to meet nutritional needs by mouth secondary to tumor burden, surgical changes, or treatment toxicity, numerous studies found inconsistent effects on nutritional status, mortality, and QOL when comparing prophylactic feeding tube placement to placement upon indication [13]. For those undergoing concurrent chemoradiotherapy, there is not sufficient evidence to determine a standard enteral feeding intervention at this time and additional investigation is needed [14].

Personalized dietary counseling by a registered dietitian has been shown to provide consistent beneficial effects on energy and protein intake, nutritional status, and quality of life when compared to no standard nutrition advice or ad libitum intake [13]. Registered dietitians are able to effectively calculate individual nutritional requirements, develop and modify appropriate nutrition regimens to achieve those requirements, and counsel patients to create personalized plans to enhance compliance [13]. The current study demonstrates that compliance to nutrition interventions results in significant protection from disease progression, supporting the need for routine and early nutritional intervention in the head and neck cancer patient population.

Locoregional progression is the leading cause of death in patients suffering from squamous cell carcinoma of the head and neck region. Although chemoradiotherapy is effective in obtaining locoregional control, treatment interruptions and dose reductions may impact the efficacy of these therapies

[20]. Early nutrition intervention can improve and preserve nutritional status and mitigate treatment toxicities, which may assist in completion of treatment in the expected timeframe. Prolongation of treatment duration is a significant independent predictor of locoregional progression in head and neck cancer patients [21]. In the present study, participants that were deemed non-compliant to nutrition interventions had significantly longer treatment durations than compliant participants (26.5 vs 14.8%, $P = 0.03$).

Pretreatment weight status is also a significant predictor of locoregional progression in head and neck cancer patients [20]. In the current study, higher pretreatment BMI was associated with a 6% significantly reduced risk of death, and a 4% significant reduced risk of disease progression, which is in consensus with the current body of literature. A study by Mick et al. found that the strongest independent predictor of survival in patients with stage III or IV head and neck cancers treated with multiple modalities was pretreatment weight loss [22]. Numerous studies also found that lower pretreatment BMI is associated with inferior disease-free survival and local control rates in head and neck cancers [23].

Given BMI is a relatively crude measure of nutritional status, additional attention to body composition has been an area of interest in recent cancer research. Prado et al. found an association between solid tumor participants with sarcopenic obesity and lower functional status as compared to obese participants without sarcopenia. The present study did not find significant associations between sarcopenia and risk for death or overall disease progression. However, as previous studies have demonstrated an association between sarcopenia and lower functional status and survival and the present study discovered a high percentage of head and neck patients presenting with sarcopenia (70.9%), continued investigation into body composition and treatment outcomes would be beneficial [17].

The current study is limited by its retrospective design, which cannot infer causation. However, our findings are consistent with recent randomized control trials and contribute to the body of knowledge on nutritional interventions in head and neck cancer patients and their effect on treatment outcome [13].

Given the importance of nutritional compliance for patients undergoing definitive RT and its possible impact on outcomes, prospective studies should validate these finding and investigate possible ways to improve compliance for these patients. One possibility includes integration of nutritional apps into clinical practice which can send patient reminders to maintain their nutritional intake and optimize management of symptomology that maybe prohibiting them from being compliant. A second possibility includes investigating the role of patient's caregiver in helping improve compliance with dietary guidelines.

Overall, there is growing evidence of importance of diet and nutrition in management of head and neck cancer patients. Currently, focus on nutrition in cancer is very subjective and varies significantly across providers and health care systems. Very few oncology practices have dedicated and trained dietitians, therefore leaving nutrition counseling to either the nurse or clinician. Even in centers with dedicated dietitians, inadequate resources and high demand lead to a burdensome caseload and dietitians may only be able to see mainly "high risk" patients infrequently during the treatment course. From the experience at our institution, frequent encounters with the dietitian lead to better understanding and compliance to recommendations, which in turn can be associated with better outcomes. In conclusion, there is much to be elucidated on this complex and emerging area of research, so additional studies on nutrition and head and neck cancer, particularly studying compliance to nutrition recommendations, prevention of malnutrition, and the link between sarcopenia and OS/PFS, are warranted.

Author's contributions RK, SK, and MG conceived the study, participated in its design and coordination, and helped to draft the manuscript.
AB and MR participated in the study execution.
KPM and AA participated in the data collection.
SV performed the statistical analysis.
All authors read and approved the final manuscript.

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Compliance with ethical standards

Declarations This retrospective review was approved by the IRB at the Albert Einstein College of Medicine.

Conflict of interest The authors declare that they have no competing interests.

Abbreviations AND, Academy of Nutrition and Dietetics; ASPEN, American Society for Parenteral and Enteral Nutrition; BSA, body surface area; OS, overall survival; PFS, progression-free survival; QOL, quality of life; RT, radiation therapy

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