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Review

Altered fractionation radiotherapy in head and neck squamous cell carcinoma

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KEYWORDS

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Abstract *Introduction:* Fractionation plays a pivotal role in determining the effectiveness of radiation and follows the principle of 4 "R" of radiobiology. The various altered fractionation schedules used are hyper-fractionation, accelerated fractionation, and hypo fractionation.
Methods: We reviewed the landmark articles published in the peer reviewed journals to summarize the beneficial role of altered fractionation in the treatment of head and neck carcinoma.
Results: Hyper-fractionation definitely gives very good overall survival benefit for locally advanced head and neck patient's equivalent to survival benefit to that of concurrent chemoradiotherapy. Adding concomitant chemotherapy to altered fractionation is a logical approach to improve survival in locally advanced head and neck cancer patients, but it may be at a cost of higher toxicity. Mild hypo fractionation may be beneficial in early laryngeal cancers and may help in achieving better local control.
Conclusion: Altered fractionation is a very important treatment schema and requires the reinforcement of its use.

Contents

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Introduction

Head and neck squamous cell carcinoma (HNSCC) is a major oncologic burden in developing countries (age standardized rate of incidence of 10–30/100,000) [1]. In the developing countries 80% of these patients present with locally advanced stage [2]. The treatment practice for this group of patients varies from surgery followed by post-operative radiotherapy, radiochemotherapy, radical radiotherapy, induction chemotherapy followed by concurrent chemo radiotherapy and recently bio-radiotherapy. According to the recent evidences both chemotherapy and radiotherapy should be used in combination for such cases. In the MACH-NC meta-analysis concurrent chemo-radiotherapy was found to be the most effective approach with an absolute benefit of 6.5% in 5 years [3]. But the compliance and tolerance is a major concern with chemoradiotherapy especially in developing countries [4]. Altered fractionation is a feasible option in these patients with better safety profile compared to chemoradiotherapy. In this review we have focused on the altered fractionation schedule radiotherapy alone or with combination with other agents.

Since 1895 when X-ray was invented by W C Roentgen, radiation has been used for different malignant as well as benign conditions. But the concept of fractionation was not known. Thor Stenbeck (Stockholm, 1900) is credited to use small doses of radiation given each day to cure skin cancer [5]. This technique was subsequently called 'fractionated radiotherapy'. Later on Coutard showed that in cancers of pharynx and larynx, protracted fractionation result in better skin and mucosal tolerance, and improved tumor response [6]. Later on with the understanding of radiobiology radiation practice became more protracted and 1.8–2 Gy per fraction was found to give good local control at low normal tissue complication rates, and this practice was called conventional fractionated radiotherapy. With better understanding of 4 Rs of radiobiology the importance of different fractionation schedule came into practice. The various altered fractionation schedules used are hyper-fractionation, accelerated fractionation, hypofractionation and a combination of these. A brief overview of the various fractionation schedules is summarized in Table 1.

Hyper-fractionation

In hyper-fractionation, radiation is delivered in small dose per fraction with two or three fractions delivered per day to achieve a higher biologically effective dose to the tumor when the α/β ratio for tumor cells is greater than that for the dose-limiting, late-responding normal tissue. Hyper fractionation also induces radio-sensitization through cell-cycle redistribution. Reduction of the fraction size from 2.0 Gy to 1.1–1.2 Gy permits a 7–17% escalation in total radiation-dose without leading to a detectable increase in late normal-tissue injury. Two randomized control studies have evaluated the hyper fractionation for locally advanced head and neck cancer. RTOG 9003 was a four arm randomized controlled study that used 81.6 Gy in 68 fraction at 1.2 Gy twice daily for 5 days per week. Initial results of the study found increased local control ($p - 0.045$), and a trend toward improving DFS ($p - 0.067$) but there was no difference in Overall survival. Acute toxicity was found to increase but did not reach statistical significance [7]. The 5 year update of this study was published in 2014 which showed that hyper-fractionated radiotherapy improved local control and overall survival when compared to the conventional radiotherapy arm without increasing late toxicity [8]. The hyper fractionated schedules tried by Cummings et al. also found better tumor control at the cost of increased acute toxicity but late effects were not increased [9]. Of all the fractionation schedules evaluated in the MARCH meta-analysis the maximum benefit in the form of overall survival was for hyper-fractionation (8% at 5 years) [10]. A brief overview of the various trails evaluating hyper-fractionation schedules is summarized in Table 2.

Hyper-fractionation showed a definite trend to improve disease control and survival (OS-8% at 5 years) for locally advanced head and neck patient's equivalent or more compared to survival benefit achieved with concurrent chemoradiotherapy (OS-6.5% at 5 years). But it is not widely followed in head and neck protocols due to logistic reasons in implementing the twice daily schedule. However, recently different institutes are attempting to use hyper fractionation with concurrent chemotherapy as well.

Accelerated fractionation

From the understanding of radiobiology it was known that after a certain period of radiotherapy known as lag phase the resistant tumor clonogens start accelerated repopulation. Therefore an incremental dose of 0.6 Gy is required after the certain lag phase of 4 weeks to counter the accelerated repopulation to achieve tumor control. The concept of accelerated fractionation is to complete radiotherapy within 4 weeks so as to overcome this accelerated repopulation. There are different types of accelerated fraction schedules, the first group, pure accelerated fractionation regimens, reduce the overall treatment time without concurrent changes in the fraction size or total dose. But there are hybrid accelerated fractionation schedules which reduce the overall treatment time with changes in other variables such as fraction size, total dose, and time distribution. Three types of hybrid accelerated fractionations have been used Type A consists of an intensive short course of treatment in which the overall duration is much shortened with a substantial decrease in the total dose. In types B and C, the duration of treatment is more modestly shortened

Table 1 Brief overview of the various fractionation schedules.

Type of fractionation	Rationale	Overall treatment time	Dose per fraction	Total dose	Acute toxicity	Late toxicity
Hyper fractionation	Difference in rate of repair by normal tissue and tumor Radiobiology: re-oxygenation, re-distribution	Same	Generally 1.2–1.5 Gy/fraction	Increased by 7–17%	Increased	Reduced
Accelerated fractionation	Counter accelerated repopulation Radiobiology: repopulation	Reduced	1.8–2 Gy/fraction	Same or reduced	Increased	Same/increased
Hypo-fractionation	Useful in tumors with low alfa/beta and normal tissue with high alfa/beta In cases of palliation when long term toxicity is not a concern Radiobiology: repair, repopulation	Reduced	> 2.2 Gy/fraction	Reduced	Same	Increased

Table 2 Summary of trials comparing conventional vs. hyper fractionation in head and neck malignancies.

Author/year	Nature of trial	Number of patients	Outcome	Toxicity
Bourhis/2006 MARCH metaanalysis [10]	Meta-analysis	6515	Absolute survival benefit at 5 years Hyper fractionated radiotherapy – 8%	–
Beitler/2014	Randomized 4 arm	1076	Survival benefit with hyper fractionation	No increase in late toxicity with hyper fractionation compared to conventional arm
RTOG 9003 [9]	Study		HR 0.81, $P = .05$	
Budach/2006 [11]	Meta-analysis	10,225	Substantial prolongation of median survival (14.2 months, $p < 0.001$) was seen for HFRT compared to CFRT No significant gain in overall survival was observed for AFRT in comparison to CFRT	–
Cummings/2006 [10]	Randomized 2 arm study	331	5 year survival (40% vs. 30%) was also improved with HF compared to CF arm	The HF arm had a greater proportion acute toxicity of grade 3 or 4 toxicity (70% vs 53%) Grade 3 and 4 late toxicity for the CF was 10.5% compared to 7.7% in the higher dose HF arm

but the total dose is kept in the same range as a conventional treatment, by the use of either split-course twice-daily fractionation (type B) or concomitant boost fractionation (type C).

In the largest trial of pure AF by Overgaard et al. (DAHANCA 6&7study), which included 1476 patients who were randomized either an accelerated regimen of six fractions of radiotherapy per week or to receive a conventional radiotherapy regimen of five fractions per week. the total dose and fraction size were same in both arms 66–68 Gy in 33–34 fractions. The analysis showed 5-year LRC, 70% in accelerated regimen vs. 60 % in conventional radiotherapy regimen ($p = 0.005$); 5-year DFS, 73% in accelerated regimen vs. 66% in conventional radiotherapy regimen ($p = 0.01$); but there was no difference in OS between the two arms [12].

In a similar trial by Overgaard et al. (IAEA-ACC study), which included more than 900 patients who were randomized either an accelerated regimen of six fractions of radiotherapy per week or to receive a conventional radiotherapy regimen of five fractions per week, the total dose was 66–70 Gy in 33–35 fractions. The analysis of data of his trial showed the 5-year loco-regional control was 42% in the accelerated group versus 30% in the conventional group (hazard ratio [$p = 0{\cdot}004$). Acute morbidity in the form of confluent mucositis was higher in accelerated group. There were no significant differences in late side-effects between the two arms [13].

Accelerated fractionation radiotherapy (type A)

The prototype of this type is continuous hyper fractionated accelerated radiotherapy (CHART). Skaldowski et al. evaluated accelerated fractionation 7 days a week including weekends [continuous accelerated irradiation (CAIR)] and conventional 5 days a week. Five-year local tumor control was 75% in CAIR group and 33% in control arm ($p < 0.00004$) [14]. Confluent mucositis was significantly high in the CAIR group (94% vs. 53%). In a large randomized, multi-center trial ($n = 908$), Overgaard et al. compared five versus six fractions of radiotherapy per week for squamous-cell carcinoma of the head and neck (IAEA-ACC study). The authors reported excellent 92% compliance with both treatment strategies. 5-year LRC, 42% vs 30% ($p = 0.004$); 5-year DFS, 50% vs 40% ($P = 0.03$); but no difference in OS (35% vs. 28%, $p = 0.07$) [13]. Hence, the authors showed the possibility of reducing overall treatment time with better local control.

Accelerated fractionation with split-course (type b) or concomitant boost (type c)

EORTC is a randomized controlled trial compared accelerated fractionation (AF) with conventional fractionation (CF) [15]. This trial included all advanced head and neck cancers except hypo pharynx with age < 75 years, WHO status 0, 1, 2 and randomized to accelerated fractionation three fractions per day at l.6 Gy per fraction. In the 1st course 28.8 Gy delivered in 18 fractions in 8 days followed by 12–14 days split and then 2nd course of 43.2 Gy in 27 fractions over 17 days up to a total dose of 72 Gy in 45 fractions over 5 weeks. At 5 years, the loco-regional control gain was 13% (from 46% in the CF arm to 59% in the AF arm; 95% CI 3–23% gain), representing a 24% reduction of the local failure rate. In patients with unfavorable T and N (N2, N3 any T, T4 any N) the benefit in favor of the AF arm was statistically significant ($P = 0.03$) with 55% loco-regional control in the AF arm versus 37% in the CF arm (18% benefit, 95% CI 3–33% benefit).

The split course accelerated radiotherapy is no more practiced in head and neck cancers as it is radio biologically inferior. The wide spread use of intensity modulated radiotherapy helps radiation oncologist to deliver concomitant boost to the tumor with very limited added toxicity and is being evaluated in many trials.

A brief summary of the various trails evaluating accelerated radiotherapy schedules in head and neck cancers is summarized in Table 3.

Altered fractionation radiotherapy vs concurrent chemotherapy

The benefit in altered fractionation led to many investigators comparing concurrent chemoradiotherapy versus altered fractionation. Chitapanarux et al. conducted a prospective randomized clinical trial to compare chemoradiation vs. accelerated hyper-fractionated radiotherapy on 85 patients [17]. The results showed that the 5-year loco-regional control rate was 69.6% in the chemoradiation arm vs. 55.0% in the accelerated hyper-fractionation arm ($P = 0.184$). The 5-year overall survival rate was 76.1% in the chemoradiation arm vs. 63.5% in the accelerated hyper-fractionation arm ($P = 0.05$).

Gupta et al. did a meta-analysis to compare the role of concomitant chemoradiotherapy versus altered fractionation radiotherapy in loco regionally advanced head and neck carcinoma [18]. In the meta-analysis he concluded that hyper-fractionation was comparable to chemoradiotherapy in terms of the hazard ratio [HR 1.13] for death. But accelerated radiotherapy with or without dose reduction was inferior to chemoradiotherapy in terms of hazard ratio for death.

In the MARCH meta-analysis it was seen that altered fractionation had more pronounced effect on local control while the effect was less pronounced in nodal control. Thus though logistically challenging hyper-fractionated radiotherapy may give similar results to that of concurrent chemoradiotherapy and may be tried in of locally advanced head and neck cancers if feasible. It may be also more useful in patients with limited nodal burden. Accelerated radiotherapy may provide better overall survival and local control than conventional radiotherapy but the results are inferior to chemoradiotherapy. But accelerated radiotherapy schedules are easier to implement than hyper-fractionated scheduled and thus may be tried on who may not be suitable for chemotherapy and in centers where implementing hyper-fractionation is difficult.

Altered fractionation radiotherapy with concurrent chemotherapy or targeted therapy

The MACH NC meta-analysis concluded that the addition of concurrent chemotherapy gives an impressive 6.5% absolute overall survival advantage [3]. The MARCH meta-analysis concluded 8% absolute overall survival benefit of hyper fractionation radiotherapy [10]. Many investigators tried to combine these two modalities to achieve a better tumor control. An Austrian trial compared the fractionation schedule of 55·3 Gy in 17 days given alone or plus concurrent Mitomycin

Table 3 Summary of trials comparing conventional vs accelerated in head and neck malignancies.

Author/year	Nature of trial	Number of patients	Outcome	Toxicity
Bourhis/2006 MARCH metaanalysis [10]	Meta-analysis	6515	Absolute survival benefit at 5 years Accelerated radiotherapy without total dose – 2% Accelerated fractionation with dose reduction – 1.7%	–
Jens Overgaard/2003 [DAHANCA 6&7] [12]	Randomized controlled trial	1485	Disease-specific survival improved (73 vs 66% for Six and five fractions, $p = 0{\cdot}01$) but not overall survival	Acute radiation morbidity was significantly higher in the accelerated fractionation group 53% vs 33% in conventional arm There was no significant difference in late toxicity between both arms
Jens Overgaard/2010 [IAEA-ACC study] [13]	Randomized controlled trial	458	At 5 years, the actuarial rate of overall survival overall survival was 35% for those in the accelerated group versus 28% for those in the conventional group	Acute morbidity was higher in accelerated radiotherapy arm while late toxicity was not different
Budach/2006 [11]	Meta-analysis	10 225	No significant gain in overall survival was observed for AFRT in comparison to CFRT	–
Björn Zackrisson/2010 [16] [ARTSCAN study]	Randomized controlled tria	750	No difference in overall survival between accelerated and conventional fractionated radiotherapy The difference in locoregional control was also not statistically significant	Acute radiation mortality was higher in accelerated radiotherapy arm when compared to conventional radiotherapy arm

C with standard fractionation alone [19]. At median follow-up of 48 months, local control and actuarial survival were significantly higher with the combined chemotherapy and altered fractionation arm. A third of the patients treated with conventional fractionation and nearly all those treated with accelerated fractionation developed grade-III mucositis. A German cooperative group compared a concomitant boost radiation regimen alone with the same regimen plus carboplatin and fluorouracil [20]. The investigators found better loco-regional control rates and survival with the combined treatment. The study also found a significantly higher frequency of chronic dysphagia resulting in feeding-tube dependency. RTOG 99-14, a phase II study accrued 84 patients of oral cavity, oropharynx, hypopharynx and larynx to concomitant boost radiation (72 Gy in 6 weeks) plus concurrent cisplatin. The authors reported 2 and 4 year loco regional failure of 33% and 36%. 2 and 4 year overall survival 70% and 54% respectively with 42% grade 3–4 late toxicity showing feasibility of combining accelerated fractionation radiation and chemotherapy [21]. Rishi et al. in a phase III trial allocated 216 patients of stage III-IVA oropharyngeal cancer to receive either chemoradiation to a dose of 66 Gy in 33 fractions over 6.5 weeks or accelerated radiotherapy with concomitant boost to a dose of 67.5 Gy in 40 fractions over 5 weeks. The authors reported similar disease control (at 2 years 56% vs. 61%) with more acute and late toxicity in the chemoradiation arm. However, compliance to radiotherapy was superior in concomitant boost with lesser treatment interruptions [22]. Subsequently a large phase III randomized study, RTOG 0129, randomly allocated 723 patients of stage III–IV (T2N2-3M0, T3-4 Any N M0, no T1-2N1 or T1N2-3) oral cavity, oropharynx, hypopharynx, or larynx to either conventional chemo-radiation 70 Gy in 35 fractions over 7 weeks or concomitant boost chemo-radiation 72 Gy in 42 fractions in 6 weeks. In an updated analysis with a median follow up of 7.9 years the trial reported no differences in overall survival, progression free survival, loco regional failure and distant metastasis rate. There were no statistically significant differences in the grade 3–5 acute or late toxicities between the two arms [23]. In another phase III trial 891 patients of locally advanced larynx, oropharynx and hypopharynx were randomly allocated to receive radiation and cisplatin without (arm A) or with (arm B) Cetuximab. Radiation regimens included 72 Gy in 42 fractions over 6 weeks, using concomitant boost or 70 Gy in 35 fractions over 6 weeks. This trial failed to find advantage of adding Cetuximab to the cisplatin based chemoradiation schedule [24]. Therefore, point should be made that the addition of chemotherapy or targeted therapy is feasible but it failed to improve outcome. This may be explained by the increased toxicity or lack of compliance.

Adding concomitant chemotherapy to altered fractionation is a logical approach to improve survival in locally advanced head and neck cancer patients, but it may be at the cost of higher toxicity. The more wide spread use of newer radiation techniques like intensity modulated radiotherapy has helped to reduce radiotherapy induced toxicity, thus making the addition of concurrent chemotherapy to altered fractionation easier.

Accelerated postoperative radiotherapy

Adjuvant radiation is often employed in locally advanced HNSCC with adverse pathologic factors [25]. Awwad et al. in an early trial of accelerated versus conventional fractionation radiation found no added impact. However, accelerated

radiation was found to be associated with improved disease control in fast growing tumors [26]. Sanguineti et al. in an attempt to evaluate accelerated adjuvant radiation randomly allocated 226 patients of locally advanced oral cavity, oropharynx, larynx, or hypopharynx, with high-risk features (pT4, SM +, N2-3, PNI +, LVI+, ECE+, subglottic extension) after surgery to either conventional radiation 60 Gy in 30 fractions vs. accelerated radiation 64 Gy over 5 weeks. The trial reported significantly increased confluent mucositis 27% vs. 50% (SS) but similar late toxicity 18% vs. 27% (NS). However, locoregional control was not different in the two arms. Point should be made of a trend to benefit for patients with radiotherapy delay >7 weeks [27]. Another recent trial randomized 279 patients of high-risk SCC larynx and oral cavity/oropharynx to receive conventional radiation 63 Gy in 35 fractions over 7 weeks vs. accelerated radiation 63 Gy in 35 fractions over 5 weeks. At 3 years loco regional control was similar between two arms (64% vs. 70%). Confluent mucositis was higher in the accelerated radiation arm but late toxicity was similar. In a planned subset analysis Locoregional control advantage was found more for patients with primary in oral cavity and oropharynx [28].

Hypo fractionation

Hypo fractionated radiotherapy is practiced mostly in the palliative setting. There is no consensus regarding the optimum dose and fraction schedule. Mohanti et al. evaluated 20 Gy in 5 fractions palliative radiotherapy (PRT) for advanced head and neck cancer patients followed by further radiation dose in responders [29]. The patients were evaluated for response after 1 month and responders (>50% objective response) were treated with further radiation equivalent to 70 Gy. Symptom relief ranged from 47% to 76% for pain, dysphagia and respiratory distress. The median OS period of 200 days and 400 days ($P = 0.001$) for palliative RT only and further radiotherapy groups, respectively. The QUAD shot study evaluated 14 Gy in 4 fractions over 2 days and repeated every 4 weeks for 3 sessions in palliative cases of head and neck [30]. The study found median overall survival of 5.7 months, median progression free survival 3.1 months.

The rationale behind hypo-fractionation in palliative setting in head and neck cancers is the delivery of higher biologically equivalent doses at shorter treatment duration, but at the risk of higher late normal tissue toxicity. The various trials that have evaluated the role of hypo fractionated palliative radiotherapy have found good response rate and good relief of symptoms with this approach. This approach is also suited in areas where there is a high burden of patients on machines especially in developed countries. The long term toxicity may not be a major concern for these patients as they may not survive that long for late toxicity to appear.

Mild hypo-fractionation is also gaining significance in early laryngeal cancers [31]. Sung et al. did a prospective phase III trial in T1, 2 glottic carcinoma in which he randomized 156 patients into conventional fractionation arm (66 Gy/33 fractions for T1 and 70 Gy/35 fractions for T2) vs. hypo-fractionation arm (63 Gy/28 fractions for T1 and 67.5 Gy/30 fractions for T2) [32]. There was no increased toxicity in hypo-fractionation arm. The 5-year local progression-free survival was 77.8% for conventional fractionation arm and 88.5% for hypo-fractionation arm ($p = 0.213$). Thus they concluded that hypo-fractionation is not inferior to conventional with a similar toxicity profile, in T1, T2 glottic carcinoma. Kumiko et al. also tried to evaluate the role of hypo-fractionation in T1-2 laryngeal and hypo pharyngeal cancers [33]. He treated 80 patients with T1 and T2 laryngeal or hypo pharyngeal cancers with definitive radiotherapy with a fraction size of 2.25 Gy. The 5-year local control rates in the entire group, larynx T1, larynx T2 and hypopharynx T1 were 85.8%, 97.6%, 70.1% and 85.7%, respectively. They had concluded than this approach improved local control in T1 laryngeal and hypo pharyngeal cases compared to historical control. The treatment was well tolerated and there was no long term grade II toxicity after a median follow-up of 47 months. Summary of various trials which used hypo-fractionation in laryngeal cancer is given in Table 4.

Thus mild hypo-fractionation may be beneficial in early laryngeal cancers and may help in achieving better local control. Properly powered randomized control trial will throw further light in this regard.

In the recent years great concern has been expressed regarding the realistic quality review of treatment practices, patient's acceptance, compliance and outcome as well as inherent difference in therapeutic response, in developing countries compared

Table 4 Summary of trials using hypo-fractionation in laryngeal carcinoma.

Author/year	Nature of trial	Number of patients	Fraction size	Local control	Toxicity
Sung/2013[32]	Phase III randomised trial – T1–2 glottic cancer	156	2.2 Gy per fraction	5-year local progression-free survival was 77.8%-conventional fractionation arm 88.5%-hypo-fractionation arm	No difference in toxicity compared to conventional arm
Kumiko karasawa/ 2013 [33]	Retrospective – T1 and T2 Laryngeal and hypopharyngeal cancers	80	2.2 Gy per fraction	5-year – larynx T1-97.6% larynx T2-70.1% hypopharynx T1-85.7%	No grade II toxicity
Rikiya Onimaru/ 2010 [34]	Retrospective – T1 laryngeal	201	2.2 Gy per fraction	91.9–3 years 89.8–5 years	1 case of severe laryngeal edema that required tracheotomy
Ana Cristina Amado/2012 [35]	Retrospective – T1, T2 laryngeal	27	2.2 Gy per fraction	At a median follow-time of 24.7 months – 100% local control	No – severe late toxicity.

to western patients [4]. The achievement of additional local control as well as overall survival benefit becomes costly because of the doubling of acute toxicity. At the same time this practice considerably increases the departmental workload. In developing countries where radiotherapy facility is far away from necessary this practice might not be very feasible.

Conclusion

The analysis of the altered fractionation schedules alone or in combination gives an additional benefit over the conventional radiotherapy practice in terms of loco regional control as well as overall survival. Hyper-fractionated radiotherapy may confer equivalent results to concomitant chemoradiotherapy. Accelerated radiotherapy alone may confer inferior results to concomitant chemoradiotherapy, but may be safely combined with chemotherapy with better radiotherapy techniques. The increase in acute morbidity and increase in workload are problems associated with altered fractionation practice. In future altered fractionation with targeted agents as well as immunotherapy is expected to confer better tumor control with limited acute and late normal tissue toxicity.

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Conflicts of interest

The authors declare that they have no conflict of interest.

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