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ORIGINAL ARTICLE **CME**

Concurrent Cetuximab and Radiation Therapy in Patients with Locoregionally Advanced Head and Neck Cancer

HC Cheng, RKC Ngan, KH Au

Department of Clinical Oncology, Queen Elizabeth Hospital, 30 Gascoigne Road, Kowloon, Hong Kong

ABSTRACT

Objective: *To retrospectively study the clinical characteristics and treatment outcomes in patients with locoregionally advanced head and neck cancer treated concurrently with cetuximab and radiotherapy.*

Methods: *Patients with locoregionally advanced head and neck cancer treated between May 2008 and July 2010 were evaluated. Cetuximab was initiated one week before and then weekly during radiotherapy treatment. The majority of patients were prescribed a radiotherapy dose of 70 Gy.*

Results: *The age of 31 patients ranged from 45 to 84 (median, 67) years and 77% were male. The majority (65%) had comorbid diseases and 35% had a Karnofsky performance status score of 70 or less. In all, 30 patients had squamous cell carcinoma and one had undifferentiated carcinoma. Primary tumour sites were larynx (n = 12), oropharynx (n = 8), oral cavity (n = 7), hypopharynx (n = 3), and maxillary sinus (n = 1). Follow-up times ranged from 5 to 31 (median, 16) months. Response rate was 80% (complete remission, 64%; partial remission, 16%). Median duration of locoregional control was not reached (1-year and projected 2-year locoregional control rates were 70% and 55%, respectively). Median progression-free survival was 13 months (1-year and projected 2-year progression-free survival rates were 51% and 40%, respectively). Median overall survival was 25 months (1-year and projected 2-year overall survival rates were 65% and 60%, respectively). Treatment toxicities of grade 3 or more included oral mucositis (52%), radiation dermatitis (26%), and infection (13%). The majority of patients (84%) received eight doses of cetuximab.*

Conclusions : *Cetuximab given concurrently with radiotherapy was well-tolerated and not associated with a significant increase in the frequency or severity of radiotherapy-induced mucositis and dermatitis. Our data demonstrated favourable tumour response rates and locoregional control duration comparable to that in the pivotal Bonner study.*

Key Words: *Carcinoma, squamous cell; cetuximab; Head and neck neoplasms; Radiotherapy; Treatment outcome*

中文摘要

西妥昔單抗和放療聯合治療局部晚期頭頸癌患者

鄭海清、顏繼昌、區國雄

目的：回顧分析接受西妥昔單抗和放療聯合治療的局部晚期頭頸癌患者有關臨床特徵及治療結果。

方法：本研究評估2008年5月至2010年7月期間的局部晚期頭頸癌患者。在進行放射治療前一星期，

Correspondence: *Dr HC Cheng, Department of Clinical Oncology, Queen Elizabeth Hospital, 30 Gascoigne Road, Kowloon, Hong Kong.*
Tel: (852) 2958 2388 ; Fax: (852) 2359 4752; Email: chcz01@ha.org.hk

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患者先接受西妥昔單抗注射，再在放射治療期間每星期注射一次。大部分病人接受70 Gy的放射治療劑量。

結果：31名病人年齡介乎45至84歲，中位數67歲；77%為男性。大部分（65%）患者同時患有其他疾病，35%患者的化療前Karnofsky體力狀況為70分或以下。30例為鱗狀細胞癌，另1例為未分化癌。原發灶的位置分別為：喉12例、口咽8例、口腔7例、下咽3例、上頷竇1例。跟進期介乎5至31個月，中位數16個月。治療反應率為80%，其中64%屬完全緩解，16%屬部分緩解。病人未達局部區域控制的中位期；一年及預測兩年的局部區域控制率分別為70%及55%。病情無惡化生存期中位數為13個月；一年及預測兩年的病情無惡化生存率分別為51%及40%。總生存期中位數為25個月；一年及預測兩年的總生存率分別為65%及60%。治療毒性達三級或以上的包括有口腔黏膜炎（52%）、輻射性皮炎（26%）及感染（13%）。大部分患者接受8個劑量的西妥昔單抗。

結論：西妥昔單抗和放療的聯合治療的耐受性好，放射治療引致的口腔黏膜炎及皮炎的頻率和嚴重性並無增加。與Bonner研究比較，本研究所得的結果顯示無論在腫瘤反應率及局部控制率方面均得到相約療效。

INTRODUCTION

Squamous cell carcinoma of the head and neck (SCCHN) region accounts for approximately 3% of all new cancers diagnosed in Hong Kong annually.[1] The progression-free survival (PFS) and overall survival (OS) for patients with locoregionally advanced SCCHN (LASCCHN) presenting with stage III to stage IVb disease remain suboptimal. Initial treatment options for patients with LASCCHN include radical surgery followed by adjuvant radiation therapy with or without chemotherapy, chemotherapy combined with radiation therapy, induction chemotherapy followed by chemoradiotherapy or radiation therapy alone.[2-6] The current standard of care for patients with LASCCHN is radical radiotherapy (RT) given concurrently with cisplatin-containing chemotherapy if not considered for radical surgery.[7,8] However, chemoradiotherapy can be associated with significant acute and chronic toxicities and may not be tolerated by patients who are elderly and those with multiple medical problems or impaired renal function.

In the pivotal international randomised study conducted by Bonner et al,[9] when compared to radiation alone, cetuximab plus radiation therapy improved locoregional control (LRC) rate, PFS and OS in patients with LASCCHN with previously untreated primary cancers of the oropharynx, hypopharynx, or larynx.[9] This study resulted in the approval of use of cetuximab in combination with radiation therapy for treating SCCHN by the US Food and Drug Administration in March 2006.

Use of cetuximab in combination with radical RT in a similar group of patients in our institution was started in May 2008. Cetuximab is a self-financed drug which costs about HK$90,000 for a full course of treatment (i.e. 8-weekly doses). Starting from December 2009, assistance from the Samaritan Fund was available. Patients with Karnofsky Performance Status (KPS) score of 70 or more planned for initial treatment of stage III, IVa or IVb squamous cell carcinoma of the larynx, oropharynx or hypopharynx in combination with RT (≥70 Gy for whom cisplatin-based chemoradiotherapy was contraindicated) were eligible to apply for assistance from the Samaritan Fund.

METHODS

This was a retrospective analysis of the clinical characteristics and treatment outcomes in patients with locoregionally advanced head and neck cancer treated concurrently with cetuximab and radiation from May 2008 to July 2010. A total of 31 patients were identified.

Curative RT to the head and neck region consisted of a seven-week continuous course (5 daily fractions per week with a fractional dose of 2 Gy). Various RT treatment techniques were used in our patients, and consisted of two-dimensional RT (n = 23), three-dimensional conformal RT (n = 6), and intensity-modulated RT (n = 2).

Cetuximab is a chimeric monoclonal antibody, which is an epidermal growth factor receptor inhibitor delivered by intravenous infusion. For our 31 patients,

administration of intravenous cetuximab was initiated one week before RT at a loading dose of 400 mg/m^2 of body surface area over a period of 120 minutes. This was followed by seven weekly 60-minute infusions of 250 mg/m^2 of body surface area for the duration of RT over seven weeks. Premedication consisted of intravenous diphenhydramine (50 mg) or an equivalent antihistamine. Before the initial dose was given, a test dose of 20 mg was infused over a 10-minute period, which was followed by a 30-minute observation period.

Monitoring and grading of adverse events (e.g. infusion reactions, mucositis, dysphagia, dermatologic toxicities including acneiform rash, diarrhoea, weight loss) were performed weekly during treatment course. In addition, routine haematological and biochemical variables (including serum magnesium, potassium, and calcium) were also performed every week during the course of treatment.

Cetuximab was withheld after first occurrence of grade-3 skin rashes and resumed at the same dose if the skin reaction resolved to grade 2. Most infusion reactions were associated with the first infusion. For grade 1 or 2 infusion reactions, the infusion rate was reduced and then maintained as such in all subsequent infusions. Cetuximab was discontinued in the event of grade 3 or 4 hypersensitivity reactions but not for radiation-related toxic effects, nor was RT delayed because of cetuximab-related toxic effects.

The Statistical Package for the Social Sciences (Windows version 15.0; SPSS Inc, Chicago [IL], US) was used for statistical analysis. Actuarial survival rates were obtained using the Kaplan-Meier method and compared with different patient groups using the log-rank test.

RESULTS

A total of 31 patients were included in the analysis, which included 24 males and 7 females (Table 1). The distribution of patients according to the year of starting treatment were : May to December 2008 (n = 8), January to December 2009 (n = 9), January to July 2010 (n = 14). The median patient age was 67 (range, 45-84) years, and the median follow-up time was 16 (range, 5-31) months, among whom 23 (74%) were smokers and 15 (48%) were drinkers. Their distributions according to KPS were: 60 to 70 (n = 11), 80 (n = 16) and 90 to 100 (n = 4), and 20 patients (65%) had medical comorbidities. The majority of patients (n = 30) had squamous cell carcinoma while only one had an undifferentiated carcinoma. The distribution of primary tumour sites included the larynx (n = 12), the oropharynx (n = 8), the oral cavity (n = 7), the hypopharynx (n = 3), and the maxillary sinus (n = 1).

The tumour stage distribution according to T and N status was as follows : T1 (n = 0), T2 (n = 6), T3 (n = 15), T4 (n = 10), N0 (n = 8), N1 (n = 6), N2a (n = 0), N2b (n = 7), N2c (n = 9), N3 (n = 1), while according to the American Joint Committee on Cancer staging it was: stage III (n = 10) and stage IV a/b (n = 21). Treatment intent was radical in all except for one elderly patient with multiple medical comorbidities, who received treatment with palliative intent for recurrent carcinoma of tongue after previous brachytherapy

Table 1. Patient characteristics and treatments.

Characteristic / treatment	No. (%) of patients
Sex	
Female	7 (23)
Male	24 (77)
Age (years)	
40 - 49	3 (10)
50 - 59	7 (23)
60 - 69	9 (29)
70 - 79	10 (32)
80 - 89	2 (6)
KPS	
60 - 70	11 (35)
80	16 (52)
90 - 100	4 (13)
Histology	
Squamous cell carcinoma	30 (97)
Undifferentiated carcinoma	1 (3)
Primary tumour site	
Oropharynx	8 (26)
Larynx	12 (38)
Hypopharynx	3 (10)
Oral cavity	7 (23)
Maxillary sinus	1 (3)
AJCC stage	
III	10 (32)
IV	21 (68)
Treatment intent	
Radical	30 (97)
Palliative	1 (3)
Reasons for choosing cetuximab	
Impaired renal function	11 (35)
Multiple medical problems/borderline general condition	7 (23)
Patient's choice	13 (42)
RT dose actually given (Gy)	
70	27 (88)
66	3 (9)
42	1 (3)

Abbreviations: KPS = Karnofsky Performance Status score; AJCC American Joint Committee on Cancer; RT = radiotherapy.

treatment with a tongue implant. Among the other 30 patients, 28 received the concurrent cetuximab and RT as upfront primary treatment while two patients were treated for postoperative gross residual disease.

In our patients, reasons for using cetuximab instead of cisplatin given concurrently with RT were: impaired renal function (n = 11), significant medical comorbidities / borderline general condition / elderly (n = 7), and patient preference (n = 13).

Regarding the cetuximab treatment, the median number of cycles received by patients was 8 (range, 6-9) cycles and there was no treatment delay in the majority of patients except in one patient who had a delay of one week. Among the 31 patients, RT doses actually received were: 70 Gy in 35 fractions (n = 27), 66 Gy in 33 fractions (n = 3), and 42 Gy in 21 fractions (n = 1). There was no RT treatment delay in 28 patients (91%) while two (6%) had treatment delay of 2 days, and one (3%) had a treatment delay of 7 days.

Most treatment-associated toxicities were of grade 1 to 2 (Table 2). Weight loss occurred in 27 patients (87%) with a median absolute and percentage weight loss of 2 (range, 0-9) kg and 4% (range, 0-15%), respectively. Tube feeding was undertaken in eight (26%) of the patients.

Hypomagnesemia occurred in seven (23%) of the patients. Grades 2 versus 3 or higher-grade radiation dermatitis occurred in 11 (36%) and 8 (26%) of the patients, respectively. Grades 2 versus 3 or higher-grade oral mucositis occurred in 11 (35%) and 16 (52%) of the patients, respectively. Acneiform skin rashes occurred in 22 (71%) of the patients, which included grade 1 in 15 patients and grade 2 in 7.

A complete response was observed in 20 (64%) of the patients, while partial response was noted in 5 (16%). The overall response rate (i.e. either complete or partial response) was 80%. Four patients (13%) had stable disease and two patients (7%) had progressive disease. The median duration of LRC has not been reached (the 1-year LRC rate was 70% and the projected 2-year rate was 55%; Figure 1). The median PFS was 13 months (1-year PFS was 51% and projected 2-year PFS was 40%; Figure 2), while the median OS was 25 months (1-year OS was 65% and projected 2-year OS was 60%; Figure 3). When compared with other primary sites, patients with carcinoma of the oral cavity had inferior durations of LRC (Figure 4), PFS (Figure 5), and OS (Figure 6). Patients with higher nodal stages had lower OS. Patients with a grade-2 or higher acneiform rash appeared to have better OS compared to those with no rash or grade-1 skin rash. Patients with a KPS score of 80 or more had better OS those with a KPS score of less than 80 (Table 3).

Table 2. Patients experiencing various side/adverse effects.

Adverse event	% of patients		
	All grades	Grade 2	Grades 3-4
Mucositis	100	35	52
Radiation dermatitis	100	36	26
Acneiform rash	71	23	0
Weight loss	87	16	3
Infusion reaction	6	6	0
Infection	13	0	13
Leucopenia	16	10	0
Neutropenia	16	3	0

DISCUSSION

In the pivotal international randomised study conducted by Bonner et al published in 2006,[9] cetuximab-plus-RT significantly improved the median duration of LRC (24 vs. 15 months, p = 0.005), median PFS (17 vs. 12 months, p = 0.006), and median OS (49 vs. 29 months, p = 0.03) when compared to RT alone after a median follow-up time of 54 months. According to an update of the Bonner study published in 2010,[10] the five-year OS was 45% in the cetuximab-plus-RT group and 36% in the RT-alone group (absolute gain in OS of 9%). In the meta-analysis of chemotherapy in head and neck cancer (MACH-NC) published in 2009,[11] among the 50 concomitant chemo-RT trials the absolute survival benefit of adding concomitant chemotherapy to RT at five years was 6.5%. In the meta-analysis of randomised trials comparing conventional RT with

Table 3. Summary of results according to subgroups.

Subgroup	No. of patients	1-Year overall survival (%)
Nodal staging		
N0	8	100
N1	6	80
N2b	7	52
N2c	9	40
N3	1	0
Grading of acneiform rashes		
Grade 1 or less	24	62
Grade 2 or more	7	70
Karnofsky Performance Status score		
60-70	11	42
80-100	20	78

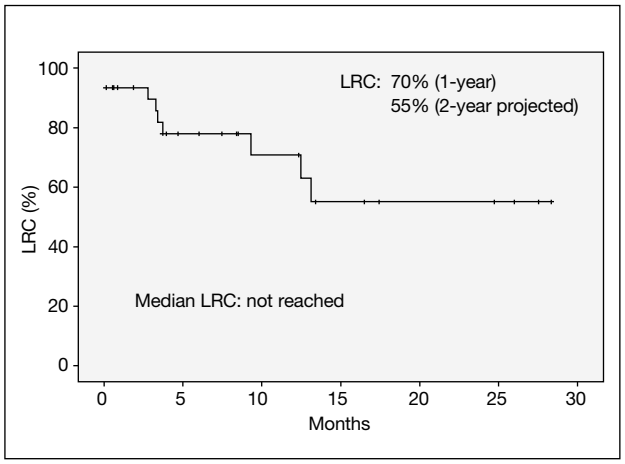

Figure 1. Locoregional control (LRC) of the whole group.

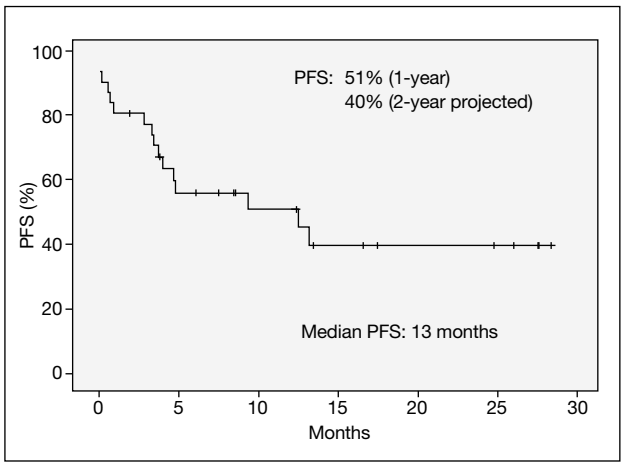

Figure 2. Progression-free survival (PFS) of the whole group.

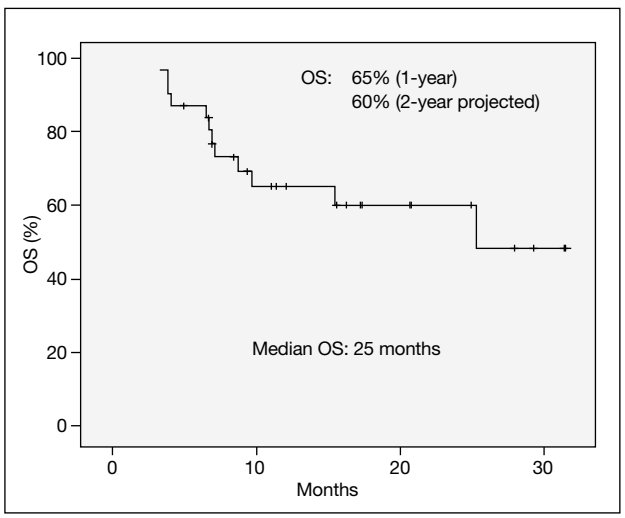

Figure 3. Overall survival (OS) of the whole group.

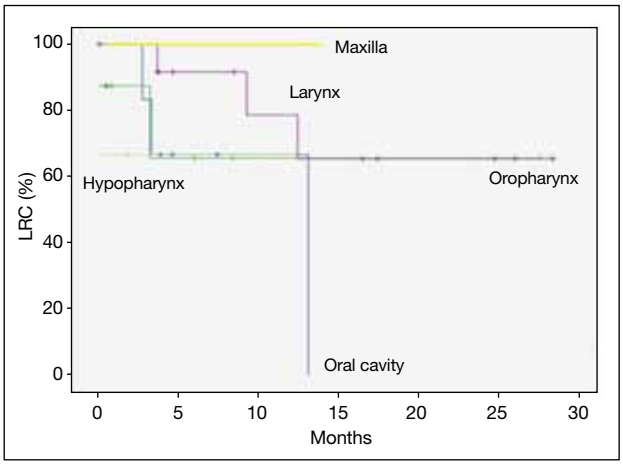

Figure 4. Locoregional control (LRC) at the primary sites.

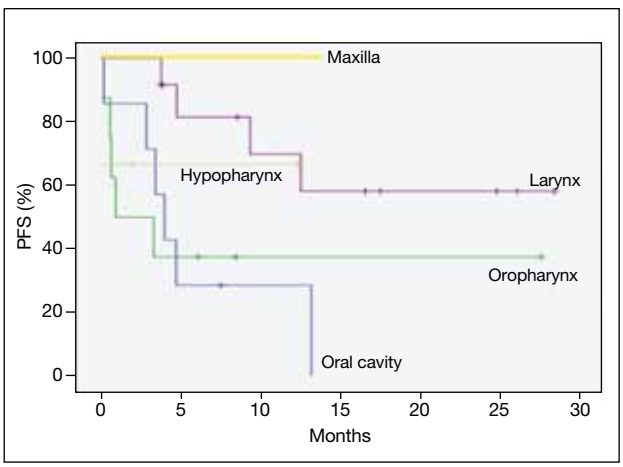

Figure 5. Progression-free survival (PFS) at the primary sites.

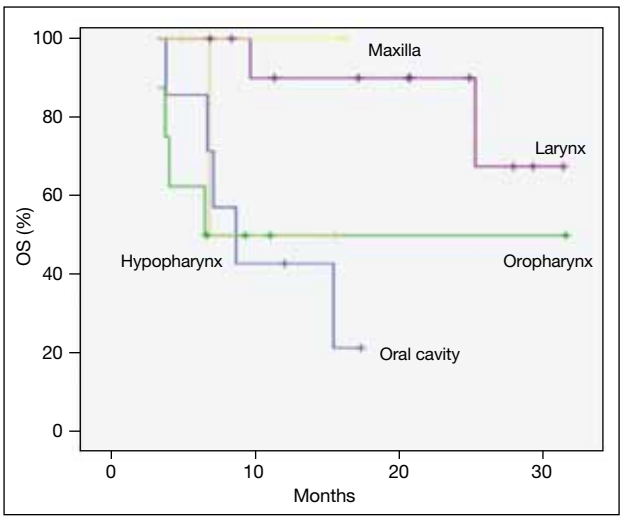

Figure 6. Overall survival (OS) at the primary sites.

hyperfractionated or accelerated RT, there was a significant survival benefit with altered fractionated RT, corresponding to an absolute benefit of 3.4% at five years.[12] The benefit at five years was higher with hyperfractionated RT (8%) than with accelerated RT (2% without total dose reduction and 1.7% with a total dose reduction), the difference being significant (p = 0.02).

In a retrospective study comparing outcomes of patients with locoregionally advanced head and neck carcinoma who were treated definitively with the addition of platinum-based chemotherapy (103 patients) or cetuximab (29 patients) concurrently with RT, at a median follow-up time of 83 months (chemoradiotherapy group) and 53 months (cetuximab-radiotherapy group), there were no significant differences in LRC, distant metastasis-free survival, disease-specific survival, and OS.[13] However, results of the phase III randomised comparison of the combination of radical RT with cisplatin and radical RT with cetuximab have not been available.

Based on the promising results employing cetuximab and RT, studies have been employed to evaluate new combinations of cetuximab and chemoradiotherapy for patients with LASCCHN.[14,15] The randomised phase III RTOG 0522 trial compared concurrent accelerated radiation plus cisplatin with or without cetuximab for patients with stage III-IV SCCHN at a median follow-up time of 2.4 years.[16] This yielded no significant differences in the respective rates of PFS (hazard ratio [HR] = 1.05, 0.84-1.29; p = 0.66; 2-year rates: 63% vs. 64%) or OS (HR = 0.87, 0.66-1.15; p = 0.17; 2-year rates: 83% vs. 80%). Cetuximab treatment is frequently associated with the development of an acneiform skin rash. The characteristic acneiform rash usually arises during the early weeks of treatment and generally resolves completely following the cessation of therapy. Results from other studies across multiple cancers suggested a correlation between OS and grading of the cetuximab-induced acneiform rash.[17] For patients treated with cetuximab in the Bonner study,[10] OS was significantly improved in those who experienced an acneiform rash of at least grade-2 severity compared to those with a grade-1 or no rash (p = 0.002). Of the 208 patients in the study who received cetuximab and had information regarding skin toxicity, 84% had a rash (61% had prominent rash and 39% had a mild rash or none). Patients exhibiting a prominent rash had more than 2.5 times longer OS than the remainder (median OS, 69 vs. 26 months; p = 0.002). In our study, a trend towards better OS was also observed in patients who developed a grade-2 acneiform rash compared to those who had a grade-1 or no rash. Development of acneiform rash may be a biomarker of an immunological response that contributes to improved outcome. The presence or absence of a cetuximab-induced acneiform rash may be used to identify patients who might benefit from more prolonged treatment with the drug or need to switch to other systemic agents.

Despite the relatively small number of patients and the retrospective nature of our study, we showed that cetuximab was well-tolerated by our patients when given concurrently with radical RT.

In our study, most patients could complete all the eight planned doses without treatment delay. Adding concurrent cetuximab had no significant adverse effects on the expected frequency and severity of RT-induced mucositis and dermatitis. Nor was it associated with any significant delay in RT treatment completion. As in the Bonner study,[9] comparable respective rates for overall response (80% vs. 74%) and LRC (55% projected at 2 years vs. 47% at 3 years) were achieved in our patients. However, our patients had lower median OS and PFS than those in Bonner's study,[9] which may be related to their being about 10 years older (median age, 67 vs. 56 years) and having a lower proportion of patients with a good KPS of 80 to 100 (65% vs. 90%). Moreover, around 35% of our patients had impaired renal function, whereas patients were required to have normal renal function to be included into the Bonner study. All patients in our study received conventional fractionated RT, whereas 74% in Bonner's study[9] received altered fractionated RT. Seven of our 31 patients had tumour arising from the oral cavity, which is a site recognised to achieve inferior treatment results. By contrast, patients with tumours arising from this site were not recruited in the Bonner study.[9] For patients with LASCCHN arising outside oropharynx, larynx or hypopharynx, the efficacy of treatment with concurrent RT and cetuximab may not be favourable. Extrapolation of the treatment results from Bonner's study to these patients may not be valid. If they are medically fit, concurrent chemo-irradiation should be preferred for these patients.

There is an increasing trend towards concurrent use of cetuximab with radical RT for patients with locally advanced carcinoma of the head and neck both locally and worldwide. Our present analysis is the first to

report on local treatment results using such an approach in Hong Kong Chinese patients having LASCCHN. Selection of appropriate patient groups for this treatment is important in order to maximise its potential clinical benefits. Proper administration of cetuximab, accurate documentation, and timely management of its treatment-related toxicities is necessary. It is currently a well-accepted therapeutic option for LASCCHN patients considered medically unfit for standard chemoradiotherapy. The National Comprehesive Cancer Network guideline recommends using cisplatin (preferred) or cetuximab in combination with concurrent RT (both category 1 recommendations) for treating patients with advanced SCCHN.[18] Cetuximab in combination with concurrent RT should also be considered for patients who do not tolerate the side-effects of chemotherapy.

CONCLUSION

Overall, cetuximab was well-tolerated when given concurrently with radical RT. Most patients could complete all eight planned doses without treatment delay. Cetuximab had no significant adverse effects on the expected frequency and severity of radiation-induced mucositis and dermatitis, nor was it associated with significant delay in completing RT treatment. As compared to patients described in the Bonner study, our patients achieved comparable responses and durations of locoregional control.

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