ALTERED FRACTIONATION RADIOTHERAPY IN LOCALLY ADVANCED HEAD AND NECK CANCERS; A REVIEW

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Abstract

Altered fractionation radiotherapy has been used to treat locally advanced head and neck cancers for many years. There are 3 types of altered fractionation; a) hyperfractionation b) accelerated fractionation, which is divided into 4 subtypes, and c) chemoacceleration. This paper is a review of the results of phase I, II, III clinical trials in each type of altered fractionation radiotherapy in locally advanced head and neck cancers. The ongoing protocol study of current EORTC and RTOG trials are also shown.

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รังสีรักษาแบบ Altered fractionation ในมะเร็งศีรษะและลำคอระยะลุกลามเฉพาะที่ ; ทบทวนบทความ

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บทคัดย่อ

รังสีรักษาแบบ altered fractionation ได้ถูกนำมาใช้รักษามะเร็งศีรษะและลำคอระยะลุกลามเฉพาะที่มาเป็นเวลานานหลายปี รังสีรักษาแบบ altered fractionation แบ่งออกได้เป็น 3 ชนิด คือ 1) hyperfractionation 2) accelerated fractionation ซึ่งแบ่งได้เป็น 4 ชนิดย่อย และ 3) chemoacceleration รายงานนี้แสดงผลการศึกษาทางคลินิกของ phase I,II,III ในแต่ละชนิดของรังสีรักษาแบบ altered fractionation ในการรักษามะเร็งศีรษะและลำคอในระยะลุกลามเฉพาะที่ การศึกษาทางคลินิกที่กำลังดำเนินอยู่ของ EORTC และ RTOG ได้ถูกนำมาเสนอไว้ในรายงานนี้ด้วยเช่นกัน

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The clinical trials in altered fractionation radiotherapy in locally advanced head and neck cancers have been studied for many years. From the year 1970's to early 1980's, the studies of altered fractionation radiotherapy were phase I,II clinical trials focusing on hyperfractionation with a limit in the number of cases and no long term follow up reported. Accelerated fractionation has been studied after 1980. Clinical phase III trials were begun in late 1980's to compare the results between altered and standard treatment regimen. After 1990, the use of concomitant chemotherapy and altered fractionation radiotherapy has been reported. By now, the clinical trials are still ongoing and getting close to draw a conclusion of the proper altered fractionation treatment regimen for locally advanced head and neck cancers.

The altered fractionation radiotherapy schedules can be divided into 3 types

1) Hyperfractionation

2) Accelerated fractionation

A) Continuous hyperfractionated accelerated radiotherapy (CHART)

B) Split course accelerated treatment

C) Concomitant boost

D) Escalating dose

3) Chemoacceleration

Hyperfractionation radiotherapy

The basic rationale of hyperfractionation regimen is to use a small dose per fraction to allow higher total dose within the tolerance of late responding tissue that can be translated into higher biological effective dose of tumor.[1]

Phase I,II clinical trials

The earlier clinical trials in phase I,II hyperfractionated radiotherapy in locally advanced head and neck cancers were limited in the number of patients and no long term follow - up reported.[2,3,4] Horiot et al.[5] collected 103 cases of locally advanced head and neck cancers treated by twice a day regimen using a dose per fraction of 1.15 Gy to 1.25 Gy up to 70 to 80.5 Gy. The acute side effects were accepted. The result showed an improvement in 5-year locoregional control rate when using a total dose of 80.5 Gy compared with less than 80 Gy (P= 0.05). However, there was no firm conclusion from this study. Meoz et al. [6] used a bid regimen of 1.1-1.2 Gy per fraction to a total dose of 60-75 Gy in 5-6.5 weeks. They found 1-year local control rate at primary site, and nodal areas being 41% and 54% respectively, and 3-year disease free survival being 40%. Parsons et al.[7,8,9] reported higher 5-year local control rate when using bid regimen of 1.2 Gy per fraction to a total dose of 74.5-76.8 Gy compared to historical control by conventional regimen in the treatment of locally advanced head and neck cancers, especially in hypopharyngeal and T2-3 laryngeal carcinoma. The most famous study of hyperfractionation phase I,II clinical trial was the RTOG protocol 83-13.[10] This study used a bid regimen of 1.2 Gy per fraction with a total dose of 67.2, 72, and 76.8 Gy. The data showed 2-year locoregional control rate 25%, 37%, and 42% respectively with no significant difference in major late side effect and survival between 3 arms. The locoregional control rate using the bid regimen with a total of 67.2 Gy was comparable to 66-74 Gy of conventional fractionation. After continuing the study for the period of time, the arm with a total dose of 81.6 Gy was added. The final conclusion

showed no significant difference in acute side effect and survival rate at 1 or 2 years between 4 arms. However, 2-year locoregional control rate from the 67.2 Gy arm was significantly lower than the other three arms (25% vs 43-45%, P= 0.01) and more significant side effect noted when using the interval between fraction less than 4.5 hours.[11]

Phase III clinical trials

Many phase III clinical trials were studied to compare the results of treatment between hyperfractionation and conventional radiotherapy in locally advanced head and neck cancers. The RTOG protocol 79-13[12] showed no significant difference in 2-year locoregional control and survival rate between two treatment arms, using 1.2 Gy per fraction, bid, to a total of 60 Gy in 5 weeks versus conventional fraction to a total dose of 66-73.8 Gy in 7-8 weeks. For severe acute mucositis and major late side effect, no significant difference noted either. However, there was a significant difference in acute and late side effect when compared the interval between fraction more than 4.5 hours to lesser. From the reports of Horiot[13] and Datta[14]; the locoregional control rate was better in the hyperfractionation than conventional fractionation. Sanchiz et al.[15] noted that the median duration of response to treatment or survival rate using hyperfractionation or concurrent chemoradiotherapy was better than conventional radiotherapy alone. Pinto et al.[16], found the subset of patients with oropharyngeal carcinoma stage III - IV who had a better trend to increase survival when treated by hyperfractionated regimen. This group was those who had Karnofsky performance status more than 70, nodal status N_{0-1}, and non base of tonque carcinoma. The trend to increase survival was noted in patient with stage III, not in stage IV. From EORTC Protocol 22791,[17] Horiot et al. noted that 5 - year local control rate was better for oropharyngeal carcinoma (which excluded base of tonque lesion) stage T_3, N_{0-1} (not for T_2) , treated by hyperfractionated radiotherapy. Although the survival rate was not significantly different, increasing in locoregional control showed a trend to increase survival in the patient treated by hyperfractionated regimen. From those reported above, severe acute mucosal reaction was noted when using hyperfractionated regimen, but no significant difference in major late side effect from conventional fractionation.

Accelerated fractionation

The basic rationale for accelerated fractionation is that the reduction in overall treatment time will decrease the opportunity for tumor cell regeneration during treatment therefore increase in the probability of tumor control for a given total dose. This can be translated into the gain in therapeutic ratio, while the acuted side effect remains tolerable and no change in late side effect.[1]

Accelerated fractionation is divided into 4 types:

Type A Continuous hyperfractionated accelerated radiotherapy (CHART)

Type B Split - course accelerated fractionation schedules

Type C Concomitant boost regimen

Type D Escalating dose regimen

Type A CHART

Phase I,II clinical trials

From the reports of Penacchia[18], Svoboda[19], Olmi[20] and Lamb[21], using a regimen of 1.7-2.3 Gy per fraction, tid, with an interval between fraction ranging from 3 to 6 hours, to a total dose of 48-55 Gy in 9-12 days, the results of treatment were not better than that of the previous one from conventional fractionation, except more severe mucositis was detected. Sanders et al.[22], using a 1.4 -1.5 Gy per fraction, tid, 6 hours interval, to a total dose of 50.4 - 54 Gy in 12 days, found complete response rate at primaries and nodes 90% , and 3 - year locoregional control rate around 49%, both of which were significantly better than previous data of conventional fractionation. Although severe mucositis was still detected, decreasing in late xerostomia was also noted.

Phase III clinical trials

Awwad et al[23] found no significant difference in 3 - year disease free survival between accelerated fractionation by using a dose 1.4 Gy per fraction, tid, 6 days/ week, to a total dose of 42 Gy in 30 fractions in 11 days and conventional fractionation of 50 Gy in 5 weeks for postoperative radiation treatment in locally advanced T_3, T_4 ; N_{0-2} head and neck cancers. Concerning about tumor labelling index (TLI) of more than 10.4%, the higher survival probability was noted in accelerated fractionation. The MRC trial[24] reported no difference in locoregional control , disease free interval and survival between accelerated and conventional fractionation, but the margin of primary control was favored in the accelerated fractionation arm. The subgroup which showed a greater response in the accelereted fractionation treatment was a younger case and more advanced primary lesion of laryngeal carcinoma (as shown in table 1). A decreasing in severe late morbidity was also noted in the accelerated fractionation arm.

Table 1 Larynx, % local control

	CHART	Conventional fraction	P value
$T_{1,2}$	72	72	no significant
T_3	66	32	0.001
T_4	73	22	0.011

The Princess Margaret trial[25] showed the result of treatment comparing between 1.45 Gy, bid, to a total dose of 58 Gy/ 4 weeks (arm A) versus 2.55 Gy once a day to a total dose of 51 Gy/ 4 weeks (arm B) as in table 2.

The significant improvement of local control in arm A was noted when tumor size was less than 4 cm. and the best improvement was shown in hypopharyngeal carcinoma.

Table 2 % local control

	arm A	arm B	P value
tumors < 4 cm.	54	42	0.04
tumors > 4 cm.	38	41	
all sized	45	40	0.16

Type B split course accelerated treatment

The rationale for split course regimen is that resting period during the course of radiotherapy will allow normal tissue to recover to decrease side effect from treatment.

Wang[26] reported an improvement in 3-year locoregional control rate of T_3, T_4 with node positive oral cavity, oropharyngeal and laryngeal carcinoma using a bid regimen of 1.6 Gy per fraction, with a resting period of 2 weeks at 38 Gy , to a total dose of 64-67.2 Gy (compared to historical control by conventional treatment).

In 1988[28], he showed the result of 3-year locoregional control using split period during twice daily fractionation compared with a twice daily, split period, followed by once a day treatment. The improvement of locoregional control in bid-bid regimen was shown in table 3

Table 3 % locoregional control (LRC)

	bid-bid	bid-qd	P value
3-year LRC	85	56	0.0013
$T_{1,2}$	97	81	0.53
$T_{3,4}$	77	47	0.017
N_0	93	46	0.00043

In proceeding ASTRO 1995, Wang reported the factors which adversely affected the local control when using split course regimen for treated T_3 oropharyngeal and laryngeal carcinoma. Those factors were; prolong gap period for more than 14 days, overall treatment time more than 45 days, total tumor dose below 67 Gy, and male gender.[28,29] The EORTC protocol 22851 designed a phase III trial[30] and compared the result treatment between conventional fractionation of 70 Gy in 7-8 weeks (arm A), versus split course regimen using 1.6 Gy per fraction, tid , with a 12-14 days rest at 28.8 Gy, to a total dose of 72 Gy in 45 fractions in 5 weeks (arm B). When excluded hypopharyngeal carcinoma, the complete response rate at 4 weeks was 59% in arm A versus 46% in arm B (P=0.032) which

referred to a 22% decreasing in locoregional failure, and a gain of 13% in 5-years survival rate over conventional fractionation. The benefit was shown in the tumor of $N_{2,3}$ with any T and T_4 with any N. This study was concluded that the specific survival had a trend to favor in arm B (P= 0.06), however, the acute and late effects were increased in accelerated fractionation treatment.

Type C Concomitant boost regimen

The concomitant boost regimen is to use a shrinking field radiation treatment added into large conventional field during the last 2-3 weeks of the treatment schedule.

Most of the phase I,II trials about concomitant boost regimen showed the acceptable result of locoregional control rate while severe mucositis was striking. [31,32,33,34] Ang et al[35] found that , a concomitant boost regimen had a benefit in 2-year actuarial survival rate when a booster dose was added during the last 2 weeks of conventional fractionation, not during the first 2 weeks or during the treatment course (table 4).

Table 4 2-year actuarial locoregional control

Arm	Primary		neck	
	RT(%)	+Surgery(%)	RT(%)	+Surgery(%)
1+2	66	73	76	80
3	79	86	75	89

2-year actuarial survival rate in arm 3 ~ 75%, arm 1+2 ~ 55% (P=0.11)

arm 1 = boost during 5-6 weeks

arm 2 = boost during first 2 weeks

arm 3 = boost during last 2 weeks

This concomitant boost regimen was used to treat the $T_{2,3}$ oropharyngeal carcinoma later[36], which resulted in 72 % 4-year locoregional control rate (increased to 81% with a surgical salvage). However, the side effect from the treatment was striking (severe mucositis longer than 6 weeks 7%, need tube feeding 10%, and moderate to severe late effect 5%). A phase III studied by Schmidth- Ulrich[37] showed a 3-year actuarial local control rate of 67% in concomitant boost regimen versus only 40% in conventional fractionation (P= 0.03). This increase in actuarial local control rate was also translated into the gain in actuarial disease free survival (64% vs 40%, P=0.04). Johnson et al. [38] found the improvement in actuarial local control rate using concomitant boost regimen in the tumor which had a volume more than 30 cm^3. The RTOG protocol 88-09[39] compared the result of treatment between split course accelerated hyperfractionation and concomitant boost accelerated fractionation.

No significant difference in locoregional control, disease free survival and survival noted between 2 treatment regimens (2-year locoregional failure 50%, survival 50% and disease free survival 40%).

Type D Escalating dose

This type of accelerated fractionation is the regimen which increase the radiation dose progressively in each week during the treatment course. This method is assumed that normal mucosal cells can tolerate radiation treatment better than intensive treatment during the course of treatment progress, that is, the overall treatment time can be reduced whereas the total tumor dose is still the same.

Few studies with a limited number of cases were reported about this type of accelerated treatment.[40,41] The results only showed the high complete response rate in each trial. Long term followed-up was noted in one study[42] which found 3-year local control rate 60% and 3-year survival rate 73%.

Chemoacceleration

Chemotherapy was used concurrently with altered fractionation to enhance the radiation effect and improve the results of treatment. Many trials[43-48] used cisplatinum based regimen as a base line chemotherapy, which resulted in complete response rate more than 90%. Some authors reported about high morbidity rate which referred to poor treatment outcome.[45,48] Brizel et al.[49] compared the 3-year result of treatment between hyperfractionation with and without concurrent chemotherapy as shown in table 5.

Table 5 Result of treatment between $HF_X + C$ vs HF_X

	$HF_X + C$	HF_X	P value
3-year LRC	70%	40%	0.01
3-year RFS	61%	41%	0.08
3-year OS	55%	34%	0.07
Confluent mucositis	77%	75%	

* HF_X = hyperfractionation 1.25 Gy bid, total dose 75 Gy/ 6 weeks
HF_X+ C = hyperfractionation 1.25 Gy bid, total dose 70 Gy/ 6 weeks with Cisplatin 12 mg/ m^2 + 5 FU 600 mg/ m^2 on week 1,6 and 2 cycles after complete radiotherapy
LRC = locoregional control
RFS = recurrence free survival
OS = overall survival

Ongoing protocol

The current EORTC trial [50] designed 4 arms treatment of locally advanced head and neck cancer to compare between standard and hyperfractionated arms with and without concomitant chemotherapy, with 5 fluorouracil and cisplatinum being the commonest. The 4 study arms are shown below.

Arm 1	70 Gy/ 35 fx/ 7 weeks
Arm 2	80.5 Gy/ 70 fx/ 7 weeks
Arm 3	Arm 1 + CDDP x 3
Arm 4	Arm 2 + CDDP x 3

The RTOG protocol 90-03[51] was begun in 1990, comparing the result of treatment of locally advanced head and neck cancer between 4 arms study of

a) standard fractionation 70 Gy/ 35 fx/ 7weeks
b) hyperfractionation 81.6 Gy/ 68 fx/ 7 weeks (1.2 Gy, bid)
c) split accelerated fractionation 1.6 Gy, bid; total dose 67.2 Gy/ 42 fx/ 6 weeks (2 weeks rest at 38.4 Gy)
d) concomitant boost regimen 1.8 Gy/ day + 1.5 Gy boost in last 12 days; total dose 72 Gy / 42 fx/ 6 weeks.

The goal of this trial was 1080 patients.

The final results from these 2 study protocols have not been reported yet. We hope that the results from these trials will determine the direction of treatment of locally head and neck cancer in the future.

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