Review paper

Six fractions weekly as accelerated fraction radiotherapy: Is it applicable for nasopharyngeal cancer? A review

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Standard therapy for nasopharyngeal cancer (NPC) is concurrent chemoradiation. Nevertheless, therapeutic outcomes are often unsatisfactory particularly for locally advanced stage. To enhance the therapeutic outcome, we may consider using altered fraction radiotherapy. Altered fraction radiotherapy is divided into two large groups for the therapy of NPC: hyperfraction radiotherapy and accelerated fraction radiotherapy. One of the accelerated fraction regimens suitable for NPC therapy is an accelerated regimen of six radiotherapy fractions weekly. This regimen is considered safe whether using conventional 2D planning technique or advance technique. Response to radiotherapy is better owing to the decrease in overall treatment time (OTT). Furthermore, acute or late side effects for this therapy are not very different to those of standard therapy. The conclusion is that we recommend the use of an accelerated regimen of six radiotherapy fractions weekly for locally advanced stage NPC with contraindication to concurrent chemoradiation, due to the high degree of clinical outcome as well as better tolerated side effect for NPC patients, particularly for those with locally advanced stage NPC.

Key words: NPC, locally advanced stage, six fractions weekly, OTT, chemoradiation.

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Introduction

Nasopharyngeal cancer (NPC) is a nasopharyngeal epithelial cell-derived malignancy. NPC has low global incidence, only 86,691 new cases yearly, comprising 0.6% of total malignancy worldwide [1]. This malignancy is mostly distributed in Southern China and South East Asia, followed by North Africa, the Middle East, North America, and the Arctic region. Endemically, NPC is mostly associated with Epstein-Barr virus (EBV) infection, particularly with World Health Organization (WHO) histological type 2 and 3 [1–3].

NPC is a radioresponsive type malignancy [4–6]. Radiotherapy has been the therapy of choice for NPC since 1950. The use of Radiotherapy as a single modality gives a relatively high overall five-year survival rate for early stages, which ranges from 60% to 85%. However, the outcome for locally advanced stage is not as satisfying, with an overall five-year survival rate of only 37% [5–8]. Administration of chemotherapy as combined therapy with radiotherapy (concurrent chemoradiation) may improve the therapeutic ratio. Concurrent chemoradiation may improve locoregional control as well as the survival rate. For stage II NPC, concurrent chemoradiation gave a three-year local control rate equal to stage I treated with radiotherapy alone. For overall locally advanced stage, concurrent chemoradiation enhance the five-year locoregional control by as much as 30%, and thus concurrent chemoradiation for locally advanced stage gave equally good outcomes as those of early stage disease treated only with radiotherapy [8–13]. Platinum-derived chemotherapeutic drugs, particularly cisplatin, is the drug of choice to be used in concurrent chemoradiation for NPC because this drug group shows superiority compared to chemotherapeutic drugs from other groups [9–12]. Today, the standard therapy for locally advanced stage NPC is concurrent chemoradiation. Nevertheless, the outcomes still fall far short of expectations, and so methods to improve radiotherapy outcome are required, one of which is by fractionation modification (altered fraction).

The basic mechanism of altered fractions

Altered fractions should take into account cancer tissue curability as well as the effect on normal tissue. Radiotherapy has to pay attention to the precision of total dose administration (TD), the dosing of each fraction (*d*), and the number of fractionations (*n*). Some cancers show variable response: occasionally a cancer shows radiotherapy responsiveness, while others show resistance to the same modality. This is determined by the α/β ratio of the cancer [5].

Biological mechanisms that influence tumour response to radiotherapy are redistribution (cell cycle), re-oxygenation, cell repair, and repopulation,

as well as other differences of radio sensitivity [14, 15]. The cell cycle comprises four phases where Gap2 phase (G2) and mitoses phase (M) which are the most sensitive phase to radiotherapy compared to the remaining [14]. Cellular repair during those phases is lower. Cancer cells do not have an optimal self-repair ability like normal cells; therefore, cancer cells undergoing sublethal damage will die when exposed the a subsequent radiotherapy fractionation.

Cancer tissue vasculature is worse than that of healthy tissue, leading to hypoxic conditions. This interferes with the cell destruction process through indirect or free radical pathway (H^+ and OH^-), which is derived from water ionisation due to radiotherapy exposure. The hypoxic area of cancer tissue is usually located in its centre. With radiotherapy fractionation, the peripheral cancer tissue (oxide area) will be damaged and reduce the volume of cancer tissue. Other intrinsic cancer conditions may also influence the outcome of radiotherapy. Overexpression of EGFR leads to cancer radio resistance, which brings an opportunity for administration of target therapy. DNA base damage due to radiotherapy will activate p53. This activation will stimulate the cell cycle checkpoint and prevent the G1 phase from entering the synthesis phase, which leads to the cell repair process. When cell repair fails, the cell will enter the apoptotic phase [14–18].

The α and β ratio

Cellular damage due to radiotherapy results from DNA strand damage, either single or double damage (α and β ratio). This is the final biological mechanism resulting from a radiotherapy dosage [5]. Thereby, the α/β ratio is the effect value of a radiotherapy dose, which is calculated to destroy cancer cells according to a quadratic linear approach. On conventional radiotherapy dose administration (1.8–2 Gy/fraction), the tumour cells' destructive effect is higher than the late destructive effect of normal cells. Vice versa, high-dose radiotherapy (beyond 2 Gy/fraction) will cause a higher late destructive effect of normal cells. This occurs especially in cancers with a high α/β ratio. The higher cancer proliferation will lead to a higher ratio of α/β of the respective cancer. Utilisation of a high radiotherapy dose per fraction on cancers with high proliferation will cause disadvantageous effects on healthy tissue.

There are three aspects to take into account in radiotherapy dosing when considering the α/β ratio. They are normal tissue acute effects, normal tissue late effects, and the cancer tissue itself. The acute side effect is the destructive cellular responses which occur a few moments to several weeks after radiotherapy. The α/β ratio of acute side effect ranges from 7 to 20 Gy. The late side effect is the destructive cellular response responses that occur several months to years after radiotherapy. The α/β ratio of late side effects ranges from 0.5–6 Gy. On conventional radiotherapy fractionation, clonogenic cell regeneration between each radiotherapy fraction may occur optimally so as to cause minimal normal tissue damage. Today, the standard fractionation of conventional radiotherapy is five fractions weekly (one fraction each day). The dosage of each fraction is 1.8–2 Gy. Despite the difference in the α/β ratio between cancer and healthy tissue, it was determined that for the acute effect the α/β ratio of cancer tissue and normal tissue is 10 Gy while for late effect of normal tissue it is 3 Gy [5, 14]. Those threshold value of the α/β ratio was determined for use on conventional fractionation.

Accelerated fractions

An increasing radiotherapy dose has a linear correlation to the number of cancer cell deaths. The increase of radiotherapy dose per fraction may be applied to slowly developing malignancies, using a more accurate radiotherapy technique according to tumour shape (3DRT, IMRT, SRT/SBRT, SRS, VMAT, helical tomotherapy, etc).

For fast developing cancer, the choice of radiotherapy strategy is by enhancing the cumulative radiotherapy total dose. However, we must pay attention to the cancer cell accelerated repopulation phenomenon. This occurs due to prolonged radiotherapy overall treatment time (OTT), resulting in compensation of clonogenic cancer, which accelerates their regeneration during the course of radiotherapy [5, 19–21]. This phenomenon may reduce post radiotherapy locoregional control. To overcome this problem, we need to prevent the radiotherapy OTT from being prolonged [20, 21].

NPC is a cancer well known for having a relatively high α/β ratio (16 Gy). Therefore, altered fractions may be applied to NPC by decreasing the dose for each fractionation followed by administration of more than one fraction per day or accelerated OTT [5, 19, 22]. The two most famous methods for altered fractions is the hyperfraction regimen and accelerated fraction regimen. Hyperfractions can be interpreted as using a smaller radiotherapy dose per fraction compared to those of conventional fractionation, which is applied more than once daily (usually twice per day) without prolongation of OTT [5, 22]. The radiotherapy dose per fraction is 1.1–1.3 Gy. Cancer tissue can be given a higher total dose (14–30%) than conventional fractionation as long as it is given with equal OTT [22–27]. According to the RTOG 9003 study, hyperfractions gave a better five-year locoregional control result when compared to conventional fractionation [28]. Acute side effects are mostly medium to severe mucositis/pharyngitis and dermatitis [23–28]. Pharyngitis side effects will require specific nutrition intervention [25].

The principle of accelerated fractions is to shorten the OTT. The aim is to prevent a fast repopulation of tumour cells. There are two methods of accelerated fractions: hybrid accelerated fractions and pure accelerated fractions.

Hybrid accelerated fractions

This method is principally the enhancement of the number of fractions, the dose per fraction, and the total radiotherapy dose. It has become the basic method for several fractionation regimens such as CHART, CHARTWEL, concomitant boost, and dynamic fractionation [28, 29]. The two first-mentioned regimens have good tumour control outcomes, but also have severe side effects. In general,

almost all patients will require hospitalisation after having a total course of radiotherapy. The last two methods are considered equally good when compared to hyperfractions. Hybrid accelerated fractions, according to Teo *et al.*, may enhance the incidence of temporal lobe necrosis twofold compared to conventional fractionation [30]. Necrosis occurred six months after radiotherapy.

Pure accelerated fractions

The basic principal of the method is not fractionation addition but acceleration of OTT. Radiotherapy was given at 2 Gy per fraction daily. Radiotherapy can be given in seven fractions weekly (including Saturday and Sunday) or six fractions weekly (the sixth radiotherapy was given on Friday afternoon or Saturday). This regimen gave good results for three-year local control and regional control, which are above 80% [31]. For a regimen of seven fractions weekly we can expect severe side effects, as in the hybrid accelerated fraction regimen [32, 33]. Six fractions weekly is considered the best tolerated accelerated fraction method.

Accelerated radiotherapy regimen of six fractions weekly

A multi-centric study by IAEA-ACC in the year 2010 reported the use of six fractions weekly for head and neck cancer, and the result from this study was imporved locoregional control when compared to conventional fraction radiotherapy with five fraction weekly (42% vs. 30%, $p = 0.004$). The survival rate was also better in the six fractions weekly group (50% vs. 40%, $p = 0.03$), even when there are no differences in overall survival. The largest advantage is on the primary tumour compared to regional metastasis. Side effects commonly encountered in six fractions weekly radiotherapy comprise mucositis and dysphagia, but these effects are reported to be tolerable. The late effect of six fraction weekly radiotherapy did not increase [34]. The results of the study above are similar to the DAHANCA 6 and 7 studies, in which locoregional control was also better in radiotherapy with six fractions weekly compared to five fractions weekly (70% vs. 60%, $p = 0.0005$) (Table 1).

The greatest advantage is in primary tumour treatment (76% vs. 64%, $p = 0.0001$). There are no differences in terms of overall survival. The side effect of mucositis is associated more with the six fractions weekly regimen [35]. All studies from IAEA and DAHANCA 6 and 7 on head and neck cancer show improvement of locoregional control from radiotherapy with six fractions weekly.

In a small unpublished RCT study conducted in Indonesia in 2012, 17 NPC patients were divided into two groups, receiving six weekly fractions or five weekly fractions of ra-

Table 1. Accelerated fraction for nasopharyngeal cancer

Author(s)/year	Period of study (year)	No. of cases	Result(s)
Overgaard *et al.* 2010 (IAEA-ACC study)	5.2	908	The 5-year actuarial rate of LRC was 42% in the AF group versus 30% in CF group (hazard ratio [HR] 0.63, 95% CI 0.49–0.83; $p = 0.004$). Acute morbidity in the form of confluent mucositis was noted in 45 patients in the AF group and 22 patients in the CF group (2.15, 1.27–3.35); severe skin reactions were noted in 87 patients in the AF group and 50 patients in the CF group (1.91, 1.31–2.79)
Overgaard *et al.* 2003 (DAHANCA 6 & 7 study)	6.11	1485	Overall 5-year LRC rates were 70% and 60% for the AF and CF groups, respectively ($p = 0.0005$). DFS improved (73% vs. 66% for AF and CF, $p = 0.01$) but not OS. Acute morbidity was significantly more frequent with AF than with CF but was transient
Lee *et al.* 2011 (NPC-9902 study)	5	189	The AF + C group achieved significantly higher failure-free rate (88% at 5 years) than the CF group (63%; $p = 0.013$), the AF group (56%; $p = 0.001$) and the CF + C group (65%; $p = 0.027$). As compared with CF alone, the increase in late toxicity was statistically insignificant (36% vs. 20%; $p = 0.25$). Deaths due to cancer progression decreased (7% vs. 33%; $p = 0.011$), but deaths due to incidental causes increased (9% vs. 2%; $p = 0.62$). Improvement in overall survival reached borderline significance (85% vs. 66%; $p = 0.058$)
Lee *et al.* 2012 (NPC-0501 study)	2.4	803	Accelerated 6 fractions weekly radiotherapy has no benefit when combined with chemotherapy. PFS and OS is 76% vs. 80% ($p = 0.68$) and 89% vs. 88% ($p = 0.55$)
Bourhis *et al.* 2012 (GORTEC 99-02 study)	7.3	840	Head and neck cancer patient. AF + C had no benefit when compared with CF + C (HR 1.02, 95% CI 0.84–1.23; $p = 0.88$). CF + C is better than AF only
Matuschek *et al.* 2018	–	988	Meta-analysis study. Post-operative AF for head and neck cancer did not improve LRC and OS when compared to CF
Fan TY *et al.* 2013	2.11	45	Advanced technique with accelerated radiotherapy (SMART) + concurrent chemoradiation. DFS and OS was 93.3% and 95.5%, respectively
Tang JM *et al.* 2014	6.3	97	Advanced technique with accelerated radiotherapy (SMART) + concurrent chemoradiation or induction/adjuvant chemotherapy. Five years LRC, DMFS, and OS was 93.3%, 90.3%, and 91.6%, respectively

AF – accelerated fractions, CF – conventional fractions, C – chemotherapy, SMART – simultaneous modulated accelerated radiation therapy, LRC – locoregional control, DFS – disease-free survival, OS – overall survival, DMFS – distant metastases-free survival, PFS – progression-free survival

diotherapy. There were no differences in radiotherapy response even when clinically there was a tendency for better outcome on six fractions weekly for locally advanced stage NPC (stage T4, N+). Acute side effects comprising dysphagia, dermatitis, and leucopaenia were more commonly found in the six fractions weekly regimen group. The study used the conventional 2D radiotherapy technique. All patients received weekly 40 mg/m^2 concurrent cisplatin chemoradiation.

Lee *et al.* in 2011 conducted a study (NPC-9902) that compared four groups of intervention given to NPC stage T3-4 N0-1 M0, which are conventional fraction radiotherapy (CF), CF in combination with chemotherapy (CF + C), six fractions weekly radiotherapy (AF), and AF in combination with chemotherapy (AF + C). The chemotherapy given in this study was cisplatin 100 mg/m^2 every three weeks, followed by adjuvant cisplatin 80 mg/m^2 and 5 fluorouracil 5FU 1000 mg/m^2 every four weeks. The mean five-year disease-free survival was significantly higher in the AF + C intervention group compared to the remaining three groups. The greatest advantage was seen in stage T4. The incidence of side effects was the same (p = 0.59) for the AF + C and CF + C intervention groups. No incidence of temporal lobe necrosis was found in the study [36].

An opposite result occurred in the NPC-0501 study [37] with a bigger sample, involving 803 subjects. The use of radiotherapy with six fractions weekly in patients undergoing chemotherapy did not give better results when compared to conventional fraction radiotherapy combined with chemotherapy. Progression-free survival and overall survival were 76% vs. 80% (p = 0.68) and 89% vs. 88%, respectively (p = 0.55).

A similar result can be observed in the GORTEC 99-02 study [38]. The use of accelerated fraction radiotherapy in combination with chemotherapy gave no benefit when compared to conventional fraction radiotherapy and chemotherapy. Three-year progression-free survival and overall survival were as high as 34.1% vs. 37.6% (p = 0.88) and 39.4% vs. 42.6% (p = 0.60), respectively. On the other hand, the use of accelerated fractions was still inferior when compared to conventional fraction radiotherapy and chemotherapy. Three-year progression-free survival and overall survival of conventional fraction radiotherapy and chemotherapy when compared to accelerated fraction radiotherapy was as much as 36.7% vs. 32.2% (p = 0.041) and 42.6% vs. 36.5% (p = 0.040). However, this study was conducted in head and neck cancer patients (without nasopharyngeal involvement) and using accelerated fractions with hybrid accelerated fraction radiotherapy (concomitant boost).

In tumours with a high α/β ratio, the calculation for the tumour biological effectiveness dose (tBED) is 64.75 Gy. Hence, when chemotherapy is added as an adjuvant (chemoradiation), tBED will become 73.55 Gy. Meanwhile, accelerated fraction radiotherapy may give a higher tBED value, i.e. 77.1 Gy [31]. Nevertheless, the conclusion from several studies involving head and neck cancer (with or without nasopharyngeal involvement) general supports that accelerated fraction radiotherapy was no better than concurrent chemoradiation [37, 39]. Furthermore, the combination of accelerated fraction radiotherapy and chemotherapy results in a significantly increased tBED value, which may indicate a higher risk for acute radiotherapy effect. This may lead to interruption of radiotherapy which may impede the overall therapeutic result.

Despite the overall success of NPC therapy with concurrent chemoradiation in enhancing locoregional control in the previously mentioned study, subsequent NPC studies in Hong Kong (NPC-9901) and Taiwan (Cheng *et al.*) do not support the similar outcome of concurrent chemoradiation in all NPC stages [40, 41]. A subgroup analysis of the NPC-9901 randomised control trials concluded that concurrent chemoradiation enhances locoregional control particularly for stage T1-2 N2-3 M0, but not for stage T3-4 N2-3 M0. Similarly, Cheng *et al.* reported concurrent chemoradiation to be effective for stage II and III but not for stage IV. It appears that the use of six fractions of radiotherapy per week may bring greater benefits only for primary tumours of nasopharyngeal cancers (T3 or T4) when compared to nodal sites. Some studies are starting to use advanced radiotherapy techniques, which are more highly conformal for implementation of accelerated fractions [42–44].

In conclusion, opportunities are still available to apply accelerated fractions with six fractions of radiotherapy weekly for NPC stage T3-4 N–/+ M0. The range from conventional 2D radiotherapy technique to advance technique may be applied on accelerated fractions with six fractions of radiotherapy weekly.

Conclusions

Accelerated six fraction weekly radiotherapy is useful for treating NPC, particularly for locally advanced stage in which the range from conventional 2D radiotherapy technique to advance technique may be applied. Despite the relatively similar side effects from accelerated six fraction weekly radiotherapy with or without concurrent chemoradiation, compared to concurrent chemoradiation with standard fractions (five fractions weekly), we still recommend the use of an accelerated regimen of six fractions of radiotherapy weekly for locally advanced stage with contraindication to concurrent chemoradiation.

The authors declare no conflict of interest.

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