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Tumour Repopulation During Treatment for Head and Neck Cancer: Clinical Evidence, Mechanisms and Minimizing Strategies

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1. Introduction

The poor clinical results reported when radiotherapy ± chemotherapy for the treatment of squamous cell carcinoma of the head and neck cancer and other sites such as the cervix is protracted has been attributed to accelerated repopulation of the tumour (Withers 1988, Fyles 1992).

Evidence from several pre-clinical studies indicates that the response of normal and cancerous squamous cells to cytotoxic injury regardless of the cause includes a greatly increased mitotic rate.

For example, experimental data have shown that the accelerated repopulation response of squamous epithelia (Dörr 1977) is analogous to the acute response of normal tissue after injury. It is suggested (Trott and Kummermehr 1991) that squamous cell carcinomas retain some of the homeostatic control mechanisms characteristic of their tissue of origin. Similarly, data from this and other studies support the evidence that normal and cancerous squamous epithelia share the same behaviour in response to injury (Trott and Kummermehr 1991, Denham 1996, Trott 1999). Therefore, the mechanisms responsible for normal tissue repopulation may be considered relevant for tumour repopulation.

Cell proliferation studies undertaken by Dörr *et al.* showed that accelerated repopulation of human squamous mucosa begins as early as 1 week after initiation of treatment (Dörr 2002). Histologic analysis of human mucosa from head and neck cancer patients during a course of radiotherapy indicated a considerable decrease in cellular density from approximately 1,000 cells/mm to 500 cells/mm by the end of the first week of treatment. The drop in cellular density radically slowed in subsequent weeks reaching around 400 cells/mm by the end of the treatment. This observation suggests that cell loss is overcome by an accelerated proliferation initiated within the first week of treatment.

Since the effect of both radiotherapy and chemotherapy results in damage to the DNA of malignant cells and eradication of irreparably damaged cells, it is likely that prolongation of treatment results in repopulation of clonogenic/stem cells surviving either treatment. This also provides a plausible explanation for the much better patient outcomes observed in the treatment of head and neck cancer when chemotherapy is given concurrently with radiotherapy than when chemotherapy is given in a neo-adjuvant setting i.e., before radiotherapy (Munro 1995, El-Sayed 1996). Surgery can also trigger repopulation in resectable head and neck tumours from undetected tumour foci inadvertently left behind (Peters 1997).

2. Mechanisms responsible for tumour repopulation

Head and neck cancers respond to the cytotoxic effect of radiation and chemotherapy by increasing the mitotic rate of surviving stem cells in order to regrow the tumour (figure 1).

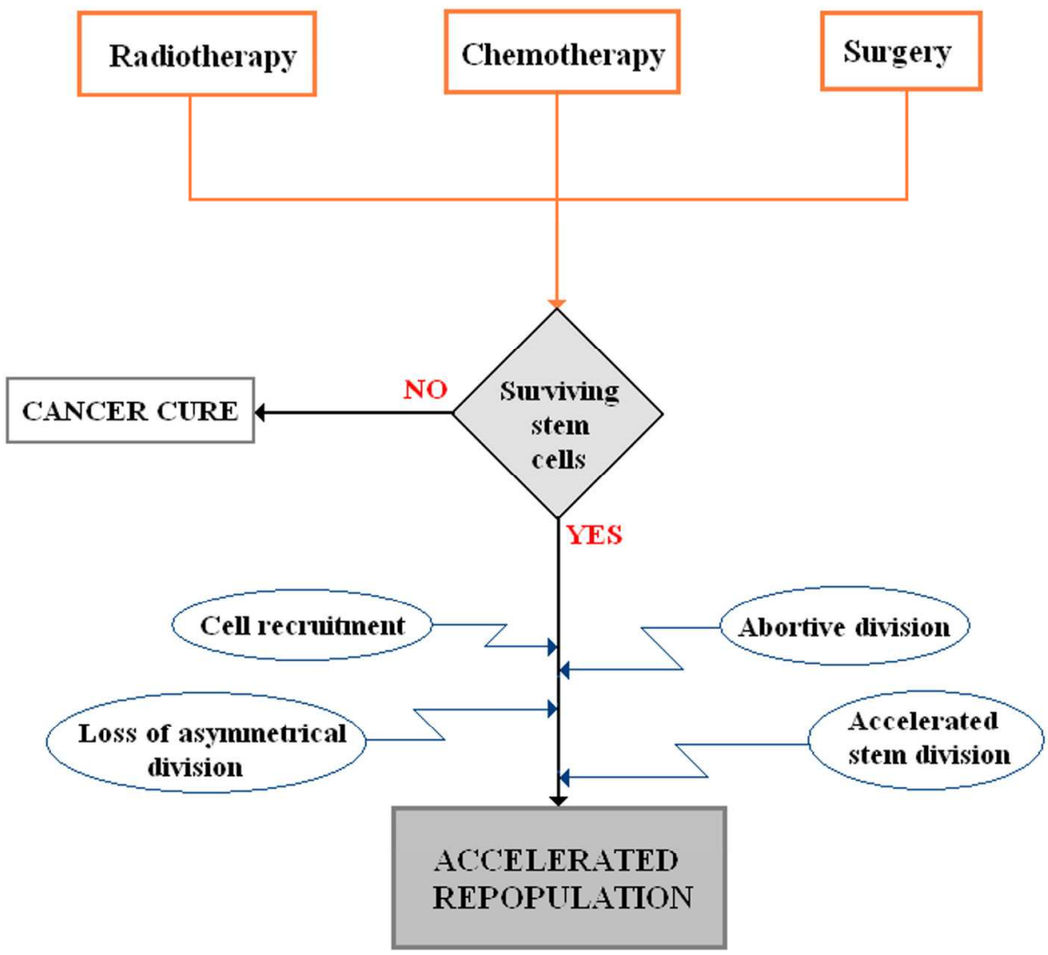

Fig. 1. Schematic diagram of the activation and the mechanisms responsible for accelerated repopulation.

Cell recruitment from the available pool of non-cycling (quiescent) cells is one plausible mechanism of tumour regrowth. In addition, other likely mechanisms, named by Dörr the three A's of repopulation, include acceleration of stem cell division, abortive division and asymmetrical loss in stem cell division. Accelerated stem cell division is a process whereby stem cells shorten the duration of the cell cycle thus resulting in a higher rate of mitosis. Abortive division is associated with loss of the limited number of cell divisions by stem cells destined to die, while asymmetrical loss in stem cell division results in stem cells dividing symmetrically into two stem cells instead of one stem cell and one differentiated cell.

While all of these repopulation processes contribute to accelerated tumour regrowth, the loss of asymmetrical division has been reported to be the most potent mechanism (Marcu 2004).

One of the latest studies looking at the mechanisms behind accelerated tumour repopulation showed that apoptotic tumour cells are the trigger for existing tumour cells to regrow (Huang 2011). The study showed, both *in vitro* and *in vivo,* that dying cells stimulate the re-growth of irradiated tumour cells more efficiently than non-irradiated cells. The mechanism of repopulation was found to be driven by the caspase 3 protease pathway. Head and neck cancer patient studies have confirmed the findings whereby high levels of caspase 3 expression are associated with a higher rate of tumour recurrence.

3. Strategies to overcome tumour repopulation

The first step to overcome tumour proliferation is to identify patients who are most likely to benefit from the strategy. Predictive assays of cell kinetic parameters and more recently, PET imaging using proliferation-specific radioisotopes can be used to identify patients with highly proliferative advanced head and neck tumours in order to tailor treatment individually (figure 2).

3.1 Pre-treatment approaches

3.1.1 Predictive assays

The ultimate aim of cancer treatment is towards its individualization because of the observed large inter-patient variability of tumour response to therapy even in patients with the same disease characteristics. Pre-treatment assessment of individual tumour parameters is a necessary first step towards this goal.

Predictive assays to evaluate the proliferative potential of individual tumours have been developed and applied with limited success in the treatment of patients. The purpose of assessing the tumour's proliferative potential is to distinguish between rapidly and slowly proliferating groups of cells within the tumour. Common methods to achieve this goal include measurements of cell kinetic parameters before treatment such as potential doubling time (Tpot) and the length of S phase (T_S) and to correlate these parameters with the treatment outcome. Measurement of kick-off time (T_K), which represents the time period from the start of radiotherapy until the initiation of accelerated repopulation, will provide a window of opportunity for adjustment of the conventional treatment schedule to that of any one of the 3 altered radiation dose fractionation schedules of (1) accelerated dose fractionation, (2) hyperfractionation or (3) hybrid hyperfractionated-accelerated radiotherapy schedules shown in randomised clinical trials to overcome accelerated tumour repopulation (discussed under Section III.2.1 below).

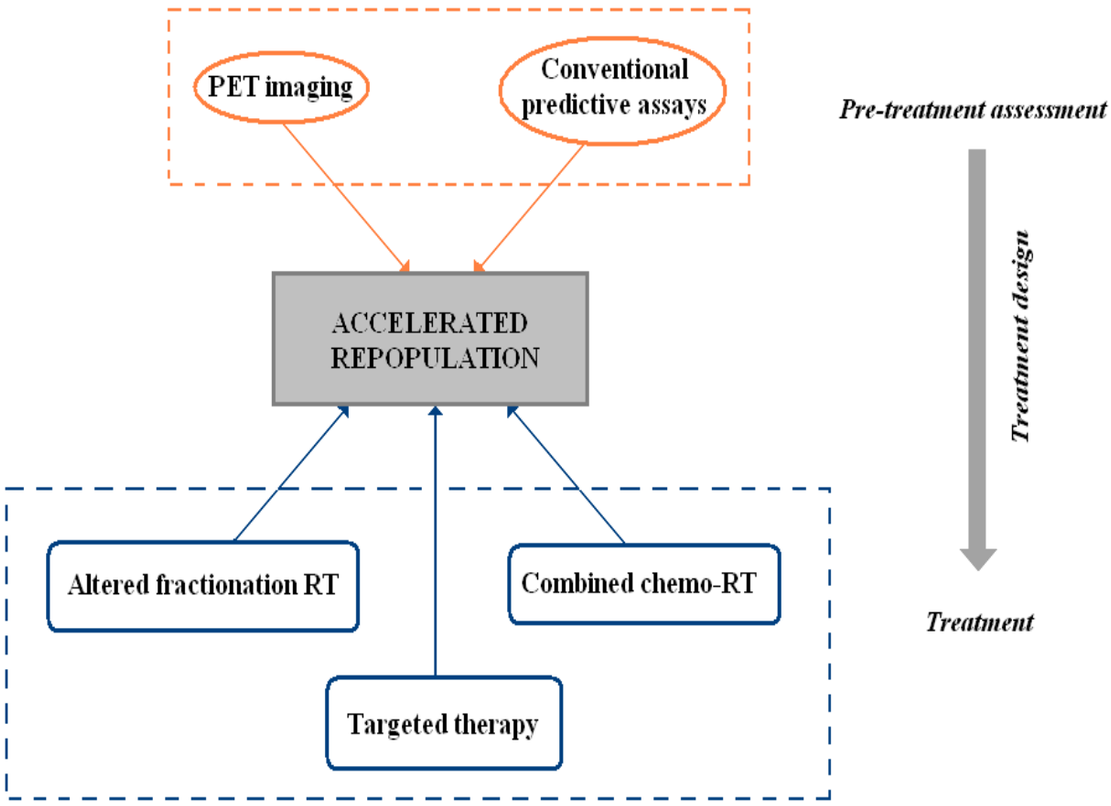

Fig. 2. Schematic diagram of pre-treatment and treatment approaches in overcoming accelerated repopulation.

Flow cytometric methods are common techniques used in the study of various pretreatment parameters of predictive value in treatment outcomes. Several studies have been undertaken to assess cell kinetic parameters and their relationships with treatment outcome (Corvo 1993, Bourhis 1996, Eschwege 1997, Begg 1999). The cytometry measurements have been based on tumour biopsies obtained after intravenous injection of bromodeoxyuridine, which is a thymidine analogue incorporated in DNA-synthesizing cells. Preliminary results obtained by Corvo *et a*l (1993) have suggested that Tpot could be a prognostic factor influencing outcome of radiotherapy in head and neck cancer patients. Although the initial results were promising, very few further studies have confirmed the utility of Tpot as a predictor of treatment outcome. Tpot was not the only parameter reported to perform poorly in predicting treatment outcomes in subsequent studies, the majority of which show that other cell kinetic parameters such as the length of S phase, and the labelling index also had poor predictive power. On the other hand, the classic clinical prognostic factors of tumour stage and nodal status were strongly associated with treatment outcomes. Begg *et al* (1999) have established that the only pretreatment kinetic parameter with some association with local control in head and neck patients was the labelling index (LI), therefore concluding that pretreatment cell kinetic measurements determined by flow cytometry techniques provide a relatively weak overall prediction of radiotherapy outcome. Table 1 presents some of the most important cell kinetic parameters characteristic of head and neck squamous carcinomas.

The proliferation-associated nuclear antigen, p105, an antigen which identifies only proliferating cells has been reported to be a potentially useful predictor for loco-regional control and survival of treated head and neck cancer patients (Fu 1994). The method is also based on flow cytometry measurements, but instead of pretreatment injections with thymidine analogues, nuclei suspensions from paraffin blocks obtained from pretreatment biopsies are prepared and processed for p105 antibody and DNA staining. Subsequent flow cytometric quantification of p105 labelling indices and DNA content are undertaken and correlated with radiotherapy outcome. Later studies (Hammond 2003) however, showed no association between p105 labelling indices, DNA ploidy and treatment outcome.

Cell kinetic parameter	Mean value & range	Publication
Cell cycle time	43.5 hours (14 – 217)	Malaise 1973
Volume doubling time	57 days (43-75)	Steel 1977
Potential doubling time (T_{pot})	4.5 days (1.8 – 5.9)	Steel 2002
Kick-off time (T_k)	21-28 days	Withers 1993
Growth fraction determined by Ki67 LI (mean/median)	27.8%	Roland 1994
Labelling index (LI)	9.6% (5-17)	Steel 1977
Cell loss factor	91%	Steel 1977
Length of the DNA synthesis phase (T_S)	11.9 hours (8.8-16.1)	Begg & Steel 2002

Table 1. Cell kinetic parameters for head and neck carcinomas

The growth factor or proliferation rate within a tumour can also be given by the marker protein Ki-67, which is a nuclear antigen associated with cell proliferation due to its presence in the nuclei of cycling cells only. A recent study evaluating the prognostic value of Ki-67 in salivary gland tumours reported better survival rates for patients with lower Ki-67 values (< 15%) than for those with Ki-67 > 15% (Vacchi-Suzzi 2010). Nevertheless, a better prognostic indicator, REPP86 (restrictedly expressed proliferation-associated protein 86), a proliferation marker expressed in several phases of the cell cycle (S, G2 and M) has been reported in a recent clinical study (Cordes 2010). Retrospective analysis of REPP86 protein-level expression in patients with laryngeal squamous cell carcinoma, with a cut-off value between high and low tumour proliferation of 25% (i.e. percentage of proliferating cells of 25%) REPP86, showed a strong correlation between proliferation and long-term outcome. Patients with low proliferating activity tumours had a 95.8% overall survival rate after 5 years, whereas those with rapidly proliferating tumours only had a 23.3% survival rate.

A property of rapidly proliferating cells is to over-express sigma receptor proteins (Bem 1991). Sigma receptors are proteins with a very complex molecular physiology and they are involved in several aspects of cancer pathology yet to be elucidated. While the overexpression of sigma receptors in proliferating cells can be up to 10-times higher than in quiescent cells (Wheeler 2000), the usefulness of sigma-2 receptors in predicting treatment outcome in head and neck cancer patients has not been convincing so far. However, based on their molecular behaviour, these receptors are currently employed in the design of novel radiotracers. Radiolabelled ligands which bind to sigma-2 receptors are trialled for PET imaging to provide a quantitative assessment of proliferative versus quiescent cells in tumours.

To date, cell kinetic measurements have not conclusively established a correlation between pretreatment parameters and treatment outcomes. While some studies have shown a relationship between kinetic parameters and radiotherapy end points, the relationship is weak and worse in predicting treatment outcomes than the classic clinical prognostic factors (TNM staging classification) or tumour volume reported in other studies (Kurek 2003).

3.1.2 Positron Emission Tomography (PET) imaging with proliferation-specific radioisotopes

As previously mentioned, cell kinetic measurements have certain drawbacks including the need to establish a correlation between pretreatment parameters and treatment outcomes and inherent delays in obtaining results which have a potential for influencing treatment outcomes. There is, therefore, a great need for developing a more reliable tool which can accurately and expeditiously identify the proliferative potential of tumours. Functional imaging techniques employing proliferation kinetics-specific markers are being trialled with promising results (for a literature review see Marcu 2011).

The most common radiopharmaceutical used in Positron Emission Tomography for functional imaging is ^{18}F-FDG (fluorodeoxyglucose), a glucose analogue which is absorbed by cells with increased metabolism (reflected in high glucose consumption) such as malignant cells. There is strong evidence of the effectiveness, specificity and sensitivity of FDG in head and neck tumours. Based on a compilation of clinical studies Chiti et al (2010) reported a range of between 93-100% sensitivity and 90-100% specificity for the primary site, validating the use of this radioisotope for tumour staging, identification of the primary site of origin (if unknown) and for assessment of treatment response.

Despite its widespread use, ^{18}F-FDG has its limitations, particularly in quantifying tumour proliferation. Tumour proliferation-specific markers were used to develop new PET radiotracers in order to enable sub-volumes to be targeted for more aggressive treatment. To date, radiotracers employed for PET imaging of cellular proliferation in solid tumours can be divided into two categories: (1) thymidine kinase-1 based radiotracers which quantify the S-phase fraction, i.e. cells undergoing DNA synthesis during tracer uptake and (2) radiolabelled sigma-2 receptor ligands which quantify the ratio of proliferating versus non-proliferating tumour cells (Mach 2009).

Reactive lymph nodes are a common source for false-positive results in head and neck cancer patients. This factor confounds the interpretation of ^{18}F-FDG PET imaging as it does not distinguish between uptake in tumour and inflammatory cells (Abgral 2009, Corry

2008). To overcome this limitation of ^{18}F-FDG PET imaging, a new marker has been investigated which allows for uptake in actively proliferating tumour cells and inflammatory cells to be differentiated. The tumour proliferation marker, 3'-Deoxy-3'[18F]-fluorothymidine (FLT) is phosphorylated by **thymidine kinase 1 (TK-1)**, an enzyme with high activity in proliferating cells. Being a key enzyme in DNA synthesis, TK-1 presents with a peak activity during the S phase of the cell cycle, thus making the radiolabelled FLT a possible candidate for the imaging of cellular proliferation.

In a recent study conducted by Troost *et al* (2010) FLT was employed to evaluate sub-volumes of tumour with high proliferation in ten patients with oropharyngeal carcinoma. The patients underwent ^{18}F-FLT-PET scans before and during radiotherapy which helped in identifying sub-volumes of high proliferative activity within the gross tumour volume, enabling the radiation dose to be escalated in the highly proliferative tumour sub-volume in the treatment plan using intensity modulated radiotherapy.

The results of a kinetic analysis involving ^{18}F-FLT were reported by Menda *et al* (2009) in eight head and neck cancer patients before and 5 days after chemoradiotherapy (i.e. after 10Gy radiotherapy and one cycle of chemotherapy). The intense initial ^{18}F-FLT uptake by the tumour showed a significant reduction after 5 x 2 Gy of radiotherapy (mean SUV_{60} decreased from 2.53 ± 0.80 to 1.31 ± 0.67 between pre-treatment and mid-treatment scans), with the changes correlating with decrease in thymidine kinase activity after treatment. Though the number of patients involved in the study was small, the data are compelling particularly if confirmed by other studies.

One of the limitations when using thymidine analogues to assess tumour proliferation with PET imaging is dictated by the level of TK-1 activity of cells in the cell cycle. While in normal cells TK-1 is active in the S-phase, thus allowing quantification of cells undergoing DNA synthesis, regulation of TK-1 varies among tumours (Schwartz 2003). To characterize the proliferation activity of oral cancers, a recent study conducted by Troost (2010b) aimed to validate ^{18}F-FLT-PET against immunohistochemical expression of the TK-1. It was shown that despite the TK-1-positive staining in most tumours, the intensity of the staining was weak and no correlation was found between TK-1 activity and ^{18}F-FLT uptake. The lack of correlation was attributed to differences in biomarker characteristics, methods of quantification and also in the resolution of the imaging modalities used. Nevertheless, the high TK-1 labelling indices (50%-80%) obtained from other tumour sites (such as breast, and non-small cell lung) should stimulate further studies of immunohistochemical staining for TK-1 in head and neck carcinomas (He 2004, Mao 2005).

As mentioned above, another group of tumour proliferation-specific radiopharmaceuticals are **radiolabelled sigma-2 receptor ligands**. PET imaging with radiolabelled sigma-2 receptor ligands was shown to offer superior tumour specific information compared to thymidine kinase-1 based radiotracer imaging (Rowland 2006, Mach 2009). While their molecular function is still not fully understood, the evidence of sigma-2 receptor overexpression in proliferating cells offered the possibility of designing new agents for PET imaging.

Both ^{11}C- and ^{18}F-labelled sigma receptor ligands have been investigated with varying results (Mach 2009). While tumour uptake studies with ^{11}C-13 showed high uptake and good image contrast (Mach 2009b), ^{11}C-labelled compounds have the disadvantage of short

half life of the radioisotope ^{11}C (20.38 min) as compared to ^{18}F (109.77 min). This drawback leads to a lower tumour to normal tissue ratio when ^{11}C agents are employed as image analysis after tracer injection is limited by the shorter half life of ^{11}C compared with ^{18}F. Tu *et al* (2007) investigated the effectiveness of fluorine-18-labelled benzamide analogues in imaging the sigma receptor status of solid tumours. Pre-clinical results demonstrated excellent tumour uptake at 5 min post-injection (2.5 − 3.7% ID/g percent injected dose per gram of tissue) which remained high 1 hour post-injection (1.2 – 2.7% ID/g) as compared to normal tissue uptake.

Another long-lived radioisotope evaluated *in vivo* is ^{76}Br, with a half life of 16.2 h and high affinity for sigma 2 receptors. A study conducted by Rowland (2006) compared the proliferation-specific imaging potential of ^{76}Br-labelled ligands with the more established ^{18}F-FLT. Although tumour uptake of the two compounds is driven by different mechanisms (^{76}Br-labelled sigma 2 receptors upregulation versus ^{18}F-FLT phosphorylation by TK-1 enzyme in proliferative tumours) a semi-quantitative comparison between their imaging characteristics allowed an assessment of their clinical utility in detecting tumours with high proliferative activity. It was found that 2 h after injection of the ^{76}Br labelled sigma 2 receptor-affinic agent, not only was tumour to normal tissue ratio (9x) higher resulting in better tumour visualization but also the metabolic clearance of non-specifically bound radioactive compounds was faster compared with ^{18}F-FLT. Although the clinical use of ^{76}Br-1 has been investigated in mammary adenocarcinoma cell lines, the relatively high tumour to normal tissue uptake ratio in head and neck cancer suggests the potential utility of ^{76}Br in tumour proliferation imaging of head and neck cancer.

A novel proliferation-specific radiotracer, ^{18}F-ISO-1, is trialled by Washington University School of Medicine in a study which is currently recruiting patients with one of the following three conditions: breast cancer, head and neck cancer and diffuse large B-cell lymphoma (ClinicalTrials.gov Identifier: NCT00968656). The primary goal of the trial is the "Assessment of Cellular Proliferation in Tumors by Positron Emission Tomography (PET) using [^{18}F]ISO-1 (FISO PET/CT)" and the evaluation of the diagnostic quality of [^{18}F]ISO-1-PET/CT images at the proposed 8 mCi dose. The trial also aims to quantify the relationship between tumour ^{18}F-ISO-1 uptake and various cellular proliferation markers and metabolic indicators such as: Ki-67, S-phase, mitotic index and sigma-2 receptors content of the tumour as secondary outcome measures.

Further studies are encouraged for the clinical validation of the existing radiotracers and for the development of new, tumour proliferation-specific PET markers for head and neck cancer.

3.2 Treatment approaches

As stated previously, an important outcome of pre-treatment assays is the identification of patients most likely to benefit from altered fractionation radiation therapy. While patients with highly proliferating head and neck tumours have been shown to gain from accelerated, hyperfractionated or combined accelerated and hyperfractionated radiotherapy alone or conventional radiation treatment schedules in combination with cytotoxic chemotherapy, patients who have tumours with low proliferation potential can be successfully treated with conventionally fractionated radiotherapy alone or in combination with cytotoxic chemotherapy.

3.2.1 Altered radiation fractionation schedules

In the treatment of head and neck cancer, three approaches to altering the schedule of conventional radiotherapy of 1.80 – 2.00 Gy week-daily dose increments have resulted in improved locoregional control without increasing late normal tissue complication rates based on randomised clinical trial data (as discussed and summarised in Table 2). These approaches are (i) accelerated fractionation dose schedules, (ii) hyperfractionated accelerated dose schedules and (iii) a hybrid of (i) and (ii) or hyperfractionated accelerated dose schedules.

An accelerated radiation dose schedule is one which is designed to shorten the duration of treatment without changing the fraction size or total dose. The ones successfully trialled have involved twice daily fractionation during some of the weekdays or once daily dose delivery six instead of the usual five days a week for conventional radiotherapy (Hlinak 2000, Overgaard 2000, see Table 2 for details).

Study	No of Patients	Experimental #	Standard #	Outcomes
(i) Hyperfractionation studies RTOG – Fu et al, 2000	1,073	81.6 Gy/68#/6.8 weeks, treating 2x/day	70 Gy/35#/7 weeks	Improved local control without increased late normal tissue complications although acute mucosal reaction enhanced.
Toronto – Cummings et al, 2000	331	58 Gy/40#/4 weeks, treating 2x/day	51 Gy/20#/4 Weeks	Improved local control without increased late normal tissue complications although acute mucosal reaction enhanced.
EORTC – Horiot et al, 1992	356	80.5 Gy/70#/7 weeks, treating 2x/day	70 Gy/35#/7 weeks	Improved local control without increased late normal tissue complications although acute mucosal reaction enhanced.
Pinto et al, 1991	98	70.4Gy/64#/6.5 weeks, treating 1x/day	66 Gy/33#/6.5 weeks	Improved local control without increased late normal tissue complications although acute mucosal reaction enhanced.
(ii) Accelerated fractionation studies Hliniak et al, 2000	395	66 Gy/33#/5.5 weeks treating 2x/day on one of 5 week days only	66 Gy/33#/6.5 weeks	Improved local control without increased late critical normal tissue complications although acute mucosal and skin reactions enhanced.
DAHANCA 6 & 7 – Overgaard et al, 2000	1,485	~ 66 Gy/33#/6 weeks, treating 6 days a week	~ 66 Gy/33#/7 weeks	Improved local control without increased late critical normal tissue complications although acute mucosal and skin reactions enhanced.

Study	No of Patients	Experimental #	Standard #	Outcomes
Skladowski et al, 2000	100	~ 70 Gy/35#/5 weeks, treating 7 days a week	~ 70 Gy/35#/7 weeks	Increased local control and overall survival but at expense of increased serious late normal tissue complications consequential to severe acute mucosal reactions.
Jackson et al, 1997	82	66 Gy/17#3-4 weeks, treating 2x/day on each of 5 week days	66 Gy/34#/6-8 weeks	Trial abandoned because of unacceptable severe mucosal toxicity preventing evaluation of treatment efficacy.
(iii) Hyperfractionated accelerated studies **A. Continuous hyperfractionated accelerated studies** TROG – Poulsen et al, 2001	350	59.4 Gy/36#/3.5 weeks treating 2x/day	66 Gy/33#/6.5 weeks	No difference in local control but reduced late normal tissue complications
GORTEC – Bourhis et al, 2000	268	63 Gy/35#/3.3 weeks treating 2x/day	70 Gy/35#/7 weeks	Improved local control without enhanced late normal tissue
UK – Dische et al, 1997	918	54 Gy/36#/2 weeks treating 3x/day	66 Gy/33#/6.5 weeks	No difference in local control but reduced late normal tissue complications
b. Split Course accelerated studies RTOG – Fu et al, 2000	1,073	67.2 Gy/42#/6.2 weeks treating 2x/day in 2 phases with 2 week break between	70 Gy/35#/7 weeks	No improvement in local control and no worsening of late normal tissue complications
EORTC - Horiot et al, 1997	500	72 Gy/45#/5 weeks treating 3x/day in 2 phases with 2 weeks break in between	70 Gy/35#/7 weeks	Increased local control but at expense of enhanced late critical normal tissue complications
c. Concomitant boost accelerated hyperfractionated studies MD Anderson – Ang et al, 2001	151	63 Gy/35#/5 weeks, treating 2x/day during last 2 weeks	63 Gy/35#/7 weeks	No statistically significant difference in local control or late normal tissue complications for whole patient group
RTOG – Fu et al, 2000	1,073	72 Gy/30#/6 weeks treating 2x/day duri8ng last 2.5 weeks	70 Gy/35#/7 weeks	Improved local control without enhancement of late normal tissue complications

Table 2. Phase III randomised trials of altered (experimental #) versus conventional (standard #) dose fractionation for radiotherapy of head and neck cancer

A hyperfractionated radiation dose schedule involves the use of lower dose fractions (typically 1.1 – 1.2 Gy) usually two times a day separated by at least 6 hrs between the dose fractions compared with the conventional 1.80 – 2.00 Gy once daily 5x/week. It is designed to enable higher total radiation doses to be delivered for improved local control without incurring increased normal tissue complication rates by exploiting the better ability of normal versus malignant cells to repair radiation damage between the multiple fractions provided a minimum time (of at least 6 hours) is allowed for the repair to occur (Fu 2000, Cummings 2000, Horiot 1992, Pinto 1991 as in Table 2). Strictly speaking the standard treatment arm of the Toronto hyperfractionation trial (Cummings 2000) does not fall within the definition of conventional dose fractionation because the treatment is delivered in 2.55 Gy once daily 5x/week and therefore incorporates a degree of acceleration but as the hyperfractionated treatment also involves the delivery of higher (1.45 Gy) than the typical 1.1 – 1.2 Gy twice daily fractions 5x/week, the study nevertheless provides data for a valid comparison of the hyperfractionation component.

By incorporating the radiobiological rationale of hyperfractionation and acceleration, hybrid hyperfractionated accelerated radiation schedules have been successfully trialled including treatment schedules of only two weeks duration albeit with up to an 18% reduction in total dose (Poulsen 2000, Bourhis 2000, Dische 1997, Fu 2000, Ang 2001 see Table 2 for details).

A dose reduction is necessary with hybrid schedules because for pure accelerated dose schedules, it has not proved possible to treat twice daily each week day nor to shorten the duration of treatment by two weeks treating daily, 7 days a week. This was because acute mucosal toxicity proved to be dose limiting which not only led to the abandonment of one of the pure accelerated dose fractionation trials but also resulted in increased rate of late normal tissue complications as a consequence of severe acute toxicity in another (Jackson 1997, Skladowski 2000, see Table 2 for details).

3.2.2 Combined chemotherapy and radiotherapy and the sequencing of the treatments

Whilst an optimal treatment regimen combining multiagent chemotherapy and radiotherapy is yet to be developed, clinical trials have established that platinum-based chemotherapy in combination with radiotherapy results in superior outcomes for locally advanced head and neck cancers compared with other cytotoxic agents in combination with radiotherapy or radiotherapy alone.

Cisplatin is among the most effective cytotoxic agents in head and neck cancer, with single agent response rates ranging from 25% to 30% (Schwachöfer 1991). Cisplatin interacts with cellular DNA to form interstrand and intrastrand crosslinks which then inhibit DNA replication and RNA transcription, leading to sublethal or lethal DNA breaks. Though inhibition of DNA synthesis implies S phase arrest, cells are blocked in the G2 phase of the cell cycle before dying (Sorenson 1990). The major mechanism of cisplatin-induced cell death is apoptosis.

In vivo studies examining the effects of combined cisplatin-radiotherapy concluded that the primary interaction between the two agents is the cisplatin-induced increased oxygenation of the hypoxic cells (Yan & Durand 1991). It was therefore suggested that cisplatin should be delivered before, rather than after irradiation. In addition, cisplatin administered daily with

fractionated radiotherapy leads to improved tumour control compared with weekly cisplatin chemoradiotherapy. Trial designs have evolved together with better knowledge of the radiobiology and the implementation of novel treatment techniques. While in the 70s cisplatin was trialled as a single-agent, in the 80s and 90s the drug was combined with conventional radiotherapy. Later, radiobiological developments on the correlation between hypoxia, repopulation and treatment failure led to new radiotherapy schedule designs which altered the conventional fractionation pattern. Nowadays, for head and neck cancer patients, cisplatin is administered concurrently with either hyperfractionated or accelerated radiotherapy, employing intensity modulated techniques (IMRT) (see Table 3).

Clinical trial/study	Trial/study design	Treatment regimen	Observations
Phase III trial ***(SAKK 10/94)*** 224 patients Ghadjar **2011**	Concomitant cisplatin and hyperfractionated radiotherapy versus hyperfractionated radiotherapy alone	**RT:** median total dose, 74.4 Gy; 1.2 Gy twice daily; 5 days per week **Chemo:** two cycles of cisplatin (20 mg/m^2 for 5 consecutive days during weeks 1 and 5)	Locoregional failure-free survival at 10 years (40% vs 32%); metastasis-free survival (56% vs 41%); cancer-specific survival at 10 years (55% vs 43%) in the combined arm vs radiotherapy alone. No difference in late toxicity. *Significantly improved treatment outcome in the combined arm.*
Clinical study 43 patients Montejo **2010**	Accelerated radiotherapy with concurrent chemotherapy	**RT:** IMRT with simultaneous integrated boost (67.5, 60, and 54 Gy in 30 daily fractions of 2.25, 2, and 1.8 Gy) **Chemo:** cisplatin 40 mg/m^2 weekly or 100 mg/m^2 every 3 weeks during radiotherapy. + weekly cetuximab (3	Complete response: 74.4%; estimated 5-year locoregional control 82%; Tolerable acute and late toxicities. *IMRT with simultaneous integrated boost with concurrent chemotherapy improved local* and *regional control.*
Phase II trial (RTOG 99-14) 84 patients Garden **2008**	Concomitant boost-accelerated radiation regimen with cisplatin	**RT:** 72 Gy over 6 weeks **Chemo:**100 mg/m^2 on days 1 and 22	2- and 4-year locoregional failure rates: 33% and 36%; 2- and 4-year survival rates: 70% and 54%
			Worst overall late Grade 3 or 4 toxicity rate 42%. *A Phase III trial comparing AFX-C plus cisplatin against standard radiation plus cisplatin has completed accrual.*

Clinical trial/study	Trial/study design	Treatment regimen	Observations
Clinical study 31 patients (larynx and hypopharynx) Lee **2007**	Concurrent chemotherapy and Intensity Modulated Radiotherapy	**RT**: median prescribed dose 70 Gy at 2.12 Gy/fraction to the PTV_{GTV}; 59.4 Gy at 1.8 Gy/fraction to the PTV of high-risk subclinical disease **Chemo:** 2 to 3 cycles of cisplatin (100 mg/m² intravenously within 2 days every 3 weeks)	The 2-year local progression-free survival: 86%; regional progression-free survival: 94%; overall survival 63%. Grade 2 (and higher) mucositis occurred in 48% of patients; all had Grade 2 or higher pharyngitis during treatment.
Phase III ***trial*** 192 patients (oropharynx) Fallai **2006**	Conventional radiotherapy (arm A) *versus* Accelerated hyperfractionated radiotherapy (arm B) *versus* Concomitant radiotherapy and chemotherapy (arm C)	**RT:** ***Arms A and C:*** 66 to 70 Gy in 33 to 35 fractions ***Arm B:*** 64 to 67.2 Gy in two fractions of 1.6 Gy every day with a 2 weeks split after 38.4Gy **Chemo:** 3 cycles of carboplatin (75 mg/m² on days 1 to 4) and 5-FU (1000 mg/m² on days 1 to 4) every 28 days	Locoregional control: Arm A+B: 20% Arm C: 48% Toxicity: Arm C showed slightly more grade 3 side effects. *Patients with advanced oropharyngeal cancers should be treated with combined chemo-radiotherapy.*

Table 3. Concurrent chemo-radiotherapy regimens employing IMRT techniques

The general consensus regarding the concurrent administration of cisplatin-based chemotherapy with radiotherapy (usually IMRT) derived from the above-presented clinical studies is in favour of chemo-radiotherapy (as compared with radiotherapy alone). Phase II trials and small studies showed that further investigations employing novel treatment regimens are warranted. Therefore, as probably expected, phase III trials have proven the superiority of the combined chemo-altered fractionation radiotherapy as opposed to radiotherapy as single agent, particularly with respect to improved locoregional failure-free survival. Since locoregional failure is still a clinical challenge in the treatment of advanced head and neck cancer, more improvements in the rate of failure-free survival are desperately needed.

In order to reduce normal tissue toxicity, a recent phase II prospective trial has investigated the tumoricidal effect of standard dose weekly cisplatin (30 mg/m² once a week over 7-8 weeks) given concurrently with radiotherapy. Despite the low-dose drug regimen (the usual dose of cisplatin is 100 mg/m² per three weekly cycle) tumour control was high, with a

locoregional control rate of 82% and a 5-year disease-free survival of 62% (Rampino 2011). Major acute toxicity (grade 3-4 mucositis) was observed in 35.2% of patients and mild late reactions occurred in 16% of patients. These results warrant further studies in a phase III randomised trial.

Beside concurrent chemo-radiotherapy, cisplatin and cisplatin-based chemotherapy have been trialled as neoadjuvant chemotherapy for definitive local treatment and for the management of distant metastases (Caponigro 2002, Posner 2005, Glynne-Jones 2007, Finnegan 2009). Induction chemotherapy has the potential to reduce the rate of distant metastases and to improve survival via the additional drug dose which targets both the systemic disease and the primary tumour (Paccagnella 2010). An overall response rate of 79% was achieved with induction chemotherapy consisting of two cycles of cisplatin on day 1, plus 5FU on days 2-5, with a 10-day interval between the two cycles (Zidan 1997). A similar result was obtained by Finnegan et al (2009), achieving an overall response rate of 75% with cisplatin- fluorouracil as induction therapy in patients with advanced head and neck cancers. A phase II randomized trial also employed a cisplatin-based neoadjuvant therapy, with cisplatin given on day 1 and 5FU-based chemotherapy on day 2, repeated every 2 weeks for four cycles (Caponigro 2002). Tumour response evaluation showed a complete response rate of 35%, which was deemed encouraging though unacceptable for further clinical implementation. Some trials have shown that the addition of 5-Fluorouracil and taxanes to neoadjuvant cisplatin further improves survival. The EORTC 24971/TAX 323 phase III trial employed cisplatin-based induction chemotherapy with and without taxanes in 358 advanced head and neck cancer patients, showing a 27% lower risk of death in the taxane arm (Vermorken 2007).

While all the abovementioned trials and studies employed injectable cisplatin, either intravenous or intra-arterial, with no significant differences in outcome between the two ways of administration (Ackerstaff 2011), physicians are striving to reduce normal tissue toxicities and unwanted side effects by trialling new ways of cisplatin administration. A recent dose-escalation trial administered oral cisplatin (CP Ethypharm®) in combination with radiotherapy to 18 head and neck cancer patients (Tao 2011). Four cisplatin dose levels were tested: 10 mg/m^2/day in 4 patients; 15 mg/m^2/day in 4 patients, 20 mg/m^2/day in 5 patients and 25 mg/m^2/day in 5 patients. Dose limiting toxicities were experienced at 25 mg/m^2 with the most frequent adverse events being gastrointestinal disorders. Therefore the dose recommended for phase II trial is 20 mg/m^2/day. Further clinical investigations are warranted to demonstrate the role of oral cisplatin in reducing the rate of adverse events.

Although chemo-radiotherapy has lately replaced radiotherapy for the management of advanced head and neck cancer, the optimal chemo-radiotherapy treatment regimen is yet to be established. While some trials showed promising results with concurrent chemo-radiotherapy, others suggest that loco-regional control can be improved with induction chemotherapy. However, meta-analyses of randomised trial data show that better treatment results are obtained when chemotherapy is administered concurrently with radiotherapy compared with chemotherapy given in a neoadjuvant setting (Munro 1995, El-Sayed 1996). Irrespective of the employed treatment, in order to overcome accelerated tumour

repopulation, treatment gaps should be avoided and the timing of chemotherapy should be well designed. Cisplatin-based chemotherapy has the potential to partially synchronise cells in the cell cycle because of cisplatin's inherent characteristic of arresting cells in the G2 phase of the cell cycle. Given that cells in late G2 have high radiosensitivity, irradiation would be more effective if started before the next mitotic cycle. Furthermore, the effectiveness of induction chemotherapy could possibly be increased by starting radiotherapy as soon as tolerable to avoid tumour repopulation negating the gain in loco-regional control.

3.2.3 Targeted therapies

A major disadvantage of chemoradiotherapy in the treatment of locally advanced head and neck cancer is the increased normal tissue toxicity, particularly to the mucosa lining the upper aero-digestive tract. Whilst younger, fitter patients may be able to be medically supported during the treatment, older patients and particularly those with medical co-morbidities may be intolerant of the treatment regimen or refuse to continue it.

Fortunately, since the general acceptance of carcinogenesis as a multi-step event involving the deregulation of molecular pathways as a result of dysfunction of oncogenes and tumour suppressor genes (Hahn & Weinberg 2002), there has been a rapid increase in the number of therapeutic agents which target the "hallmarks of cancer" (Hahn & Weinberg 2011). These hallmarks include growth factor independence and insensitivity to growth suppressor signals leading to unrestricted proliferation, evasion of apoptosis, sustained angiogenesis, immortality and tissue invasiveness and metastasis.

Targeted therapies can be defined as the agent(s) which are designed to inhibit if not eliminate one or more the characteristics or hallmarks of cancer. These target specific agent(s) should spare normal tissues such as the mucosa of the entire digestive tract from the effects of chemotherapy and of the upper aero-digestive tract from the combined effects of chemo-radiotherapy although unexpected normal tissue effects have been reported (discussed below). Despite the absence of significant normal tissue toxicity, it is likely that a combination of agents will be needed as resistance to single agents is often inevitable as judged by later reports of the initially promising results of trastuzumab, a monoclonal antibody against one of the epidermal growth factor receptors, HER 2 in the treatment of metastatic breast cancer (Jones & Buzdar 2009) and imatinib, a tyrosine kinase inhibitor which targets the oncogenic protein BCR-ABL expressed at high levels in chronic myeloid leukaemia (Gorre 2001).

With respect to the treatment of locally advanced head and neck cancer, high dose radiotherapy combined with cetuximab, a monoclonal antibody against another epidermal growth factor receptor (EGFR) HER 1 associated with signalling pathways for cellular processes such as proliferation and differentiation has been shown to improve locoregional control and survival without increasing normal tissue toxicity compared with high dose radiotherapy alone (Bonner 2006). In this landmark clinical trial, 213 patients were randomised to radiotherapy alone and 211 patients to radiotherapy with cetuximab. The addition of cetuximab to radiotherapy significantly increased 3 year loco-regional control rates from 34% to 47% and overall survival rates from 45% to 55%. The main toxicity

experienced by patients who received cetuximab was an acne-like rash and rather surprisingly sub-group analysis revealed that overall survival was better in patients with a moderate to severe (Grade ≥2) rash compared with patients who had no or a mild (Grade 0 or 1) rash. This finding opens up new possibilities for further minimizing the effects of tumour cell repopulation particularly as the improved treatment outcomes with Cetuximab in combination with high dose radiotherapy matches the best results of chemoradiotherapy without the increased normal tissue toxicity. For example, a randomized Phase III trial under the auspices of the Radiation Therapy Oncology Group (RTOG) comparing the addition of Cetuximab to accelerated radiotherapy and cisplatin chemotherapy versus accelerated radiotherapy and cisplatin chemotherapy for locally advanced head and neck cancer has been reported (RTOG 0552, 2007).

With advances in high throughput technology, gene microarray analysis is being used to predict tumour response to treatment thus heralding a future in personalised medicine (West 2007). Microarray technology used to derive a gene expression profile or signature from tumour samples has been shown to be a more powerful predictor of outcome of breast cancer in young patients than clinico-pathological staging systems (van de Vijver 2002). A small study of head and neck cancer patients treated by surgical excision reported that gene expression analysis of the tumour samples based on 205 genes discriminated between seven patients who recurred distally and eight patients who had no recurrence (Giri 2006). The implication of the study is that patients without the signature would be spared the toxicity of chemotherapy, particularly if the findings are confirmed in a larger study.

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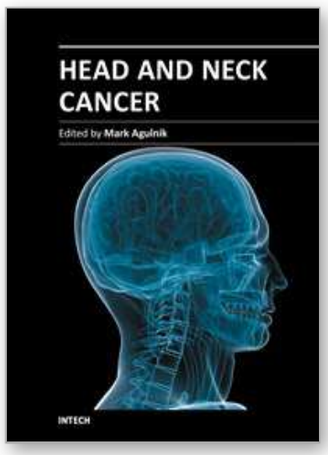

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Head and Neck Cancer provides an interesting and comprehensive overview of all aspects of head and neck cancer including overviews of the disease, basic science aspects pertaining to the disease, diagnosis, treatment and outcomes for patients with this disease. The chapters written by world renowned experts cover the entire discipline of head and neck oncology and include discussions of regional disparity is, advances in basic science understanding, advances in her radiotherapy, chemotherapy and targeted agents as well as a focus on reconstruction, prostheses, and aspects of quality of life and health outcomes. The book is designed to be both practical and comprehensive for every physician treating his complex disease.

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