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Review

Altered fractionation and combined radio-chemotherapy approaches: pioneering new opportunities in head and neck oncology

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Abstract

Squamous cell carcinoma of the head and neck (HNSCC) are increasingly treated by multimodality approaches combining surgery, radiotherapy and chemotherapy. Randomised controlled trials have demonstrated major improvements in loco-regional tumour control from altered fractionation radiotherapy, accelerated fractionation and hyperfractionation, as compared with conventional fractionation. This experience is summarised, and the limit as to how far these modifications can be taken is discussed. It is emphasised that radiation fractionation will need to be optimised separately in multimodality strategies. Combined chemotherapy and radiotherapy has also been shown in phase III trials to produce an improved survival and an improved disease control. Chemotherapy may be given as neoadjuvant, concurrent or adjuvant treatment and the biological rationales for each of these, and the data supporting them, are reviewed. Although, large meta-analyses have shown concurrent chemoradiation to be the most effective, there is still a strong rationale for trying to develop neoadjuvant and adjuvant schedules. New, more active drugs may be important in this context. As therapy is becoming more intense, a careful recording and reporting of treatment-related morbidity is a crucial element in estimating the therapeutic gain from competing therapeutic management strategies. Development of non-cytostatic drugs and individualisation of therapy using molecular prognostic markers are exciting areas of research with a great potential for improving therapy in the next decade and these are briefly discussed. Finally, a number of avenues for further research are identified.

Keywords: Head and neck; Radiotherapy; Chemotherapy; Altered fractionation; Chemo-radiation; Randomised trials

1. Introduction

Recent advances in translational and clinical research into the management of Head and Neck Squamous Cell Carcinoma (HNSCC) have led to a multidisciplinary therapeutic approach, aiming whenever possible, for organ preservation with acceptable long-term function.

Each year approximately 53 000 new cases of either oral cavity or pharyngeal cancer are diagnosed in Western Europe: patients with early stage I-II disease are proposed to receive either definitive radiotherapy or undergo conservative surgery, often resulting in equivalent disease control probabilities. In this case, the final choice between surgery and radiotherapy often depends upon the patient's preference and the expectations in terms of functional outcome. In patients with locally advanced HNSCC, more complex management strategies have developed ranging from definitive radiotherapy to a combination of surgery, radio- and chemotherapy, with a variety of radio-chemotherapy[1] regimens having been tested in clinical trials. Notwithstanding the progress in surgical techniques and in radiotherapy delivery, and the advent of new, active cytostatic drugs, treatment outcome remains characterised by three main features:

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[1] We use the term *radio-chemotherapy* to denote any strategy combining the two modalities. *Chemo-radiation* therapy, in contrast, refers to the concurrent administration of chemotherapy and radiotherapy.

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1. in patients with locally advanced tumours, loco-regional control remains unsatisfactory, with 3-year rates rarely exceeding 50–60%, irrespective of the tumour site;
2. treatment failure due to distant metastases should not be underestimated in these cases, since 1 out of 5 patients with stage III-IV disease will experience disease progression below the clavicles with or without loco-regional failure;
3. most novel approaches are characterised by a lack of differential impact on tumour and normal tissues: improvements in loco-regional control and disease-free-survival rates are often obtained at the price of increased acute and late toxicity.

Thus, despite encouraging clinical progress, there is still a clear need for further improvement of the therapeutic outcome in locally advanced HNSCC.

Altered fractionation and radio-chemotherapy combinations will be the two clinical research areas covered in this review. Both of these strategies have been shown in large randomised-controlled trials to lead to clinically important improvements in outcome. Thus, both can be considered as evidence-based medicine. However, it is also becoming clear that the ultimate treatment intensity is limited by patient tolerance and that further improvement of the therapeutic index is likely to come from the use of more sophisticated radiotherapy techniques and novel delivery schedules, and the introduction of drugs with a higher differential effect between tumour and normal tissues.

The aim of this review article is not to provide an exhaustive overview of treatment outcome after definitive radiotherapy or combined radio-chemotherapy, but rather to summarise the clinical experience with these approaches and to provide an indication of future research into improved therapy for patients with HNSCC.

2. Altered fractionation: the programming of radiotherapy

Most of the altered radiotherapy fractionation schedules tried in HNSCC since the mid-1980s have explored two types of modification [1,2]: hyper-fractionation (HFX) and accelerated fractionation (AF). There is no general consensus as to the definition of these two concepts, which, in most reports, are often defined from a direct link between the time–dose factors of a fractionated regime of radiotherapy, namely the dose per fraction, number of fractions, daily or weekly dose, overall treatment time and total dose. This has led to some confusion regarding the classification of radiotherapy schedules, especially for those close to the conventional dose intensity of 10 Gy/week that deliver a number of weekly sessions different of 5, which is the number of irradiation sessions delivered each week in conventional fractionation regimes. This frequent confusion indicates that there is a need to return to more general definitions, which directly reflect the different rationales underpinning non-conventional schedules [3]. Indeed, the concept of hyperfractionation is essentially linked to the dose-fraction and not to time. Therefore, any schedule employing a dose per fraction of less than 1.8 Gy is classified as *hyperfractionated*. In contrast, AF relates to the intensity of therapy over time and, therefore, a schedule in which the rate of dose-accumulation exceeds 10 Gy/week is classified as *accelerated*. This simple definition, besides its pedagogic character, has the advantage of being applicable to all altered fractionation schedules. In addition, it clearly separates the issues of dose/fraction from overall treatment time and total dose, which result from distinct radiobiological concepts. In a schedule using a dose per fraction different from 2.0 Gy, the rate of dose-accumulation is estimated from the total dose converted into the biologically equivalent dose in 2-Gy fractions (EQD_2) using the linear-quadratic model with an assumed α/β of 10 Gy for HNSCC [4]. Similarly, a schedule employing a dose per fraction exceeding 2.2 Gy is classified as *hypo*fractionated. Fig. 1 shows for selected altered fractionation schedules to what extent they have implemented these two rationales. Many accelerated schedules are hyperfractionated as well with some notable exceptions (Danish Head and Neck Cancer (DAHANCA) [5], continuous accelerated irradiation (AIR) [6], French Head and Neck Oncology and Radiotherapy Group (GORTEC) [7]). In addition, some hyperfractionated trials have escalated the EQD_2 while maintaining the overall treatment time equal to that of a conventional schedule and this may lead to the schedule being accelerated as well. An example is the schedule used in the European Organization for Research (EORTC) trial 22791 [1] where a total dose of 80.5 Gy was prescribed to be delivered over 7 weeks, with two daily fractions of 1.15 Gy. The EQD_2 of this schedule is 74.8 Gy and this corresponds to a rate of dose-accumulation of 10.7 Gy/week. Thus, this schedule is not only hyperfractionated, but also slightly accelerated.

Note that Fig. 1 does not illustrate the overall *treatment intensity*. For example, the continuous hyperfractionated accelerated radiotherapy (CHART) schedule is by far the strongest acceleration that has been implemented, but it is not a very 'hot' schedule, because it was necessary to reduce the total dose to 54.0 Gy in 1.5 Gy/F in order to keep early reactions at a reasonable level. Similarly, the Pinto trial was very strongly hyperfractionated, but the absorbed total dose of that schedule was only 70.4 Gy compared with 80.5 Gy for the EORTC 22791 schedule. It is a widespread misunderstanding to focus on dose per fraction or overall treatment time in isolation. Obviously, low dose per fraction is not a magic bullet in itself, total dose and overall treatment time will have to be considered as well.

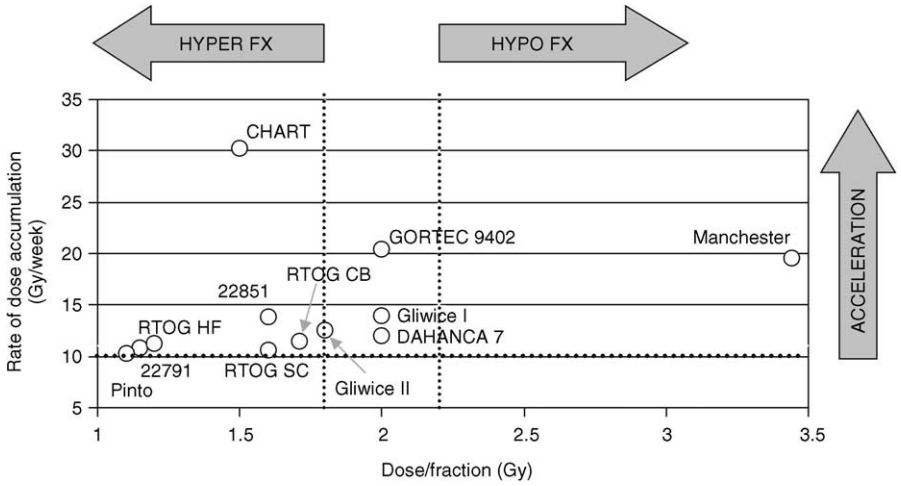

Fig. 1. Scatter plot of selected altered fractionation schedules tested in randomised controlled trials according to the dose per fraction employed and the rate of dose accumulation. The Manchester schedule is included for comparison. The trial codes and the corresponding literature references are: 22791: European Organization for Research and Treatment of Cancer (EORTC) trial [1], 22851: EORTC trial [2], CHART [15], DAHANCA [5], Gliwice I and II : CAIR with 2.0 and 1.8 Gy/F, respectively [6], GORTEC 9402 [7], Pinto [61]: Radiation Therapy Oncology Group (RTOG) RTOG 90-03 (HF: hyperfractionation, CB: concomitant boost, SC: accelerated split-course [62].

From the perspective of clinical radiobiology, it is interesting that basically all of the many schedules devised have produced a therapeutic outcome that is consistent with radiobiological modelling using parameters derived from clinical data. This may seem to be a circular argument, but what it really means is that the basic biological effect of dose, dose per fraction and overall treatment time within the range plotted in Fig. 1, is understood and may be quantified.

2.1. Tumour response to altered fractionation

The CHART trial is interesting because overall treatment time was shortened to just 12 days in the experimental arm. If the rate of dose–recovery due to tumour cell proliferation had been constant all the way from schedules of 6–7 weeks duration down to the 12 days of CHART, the biological equivalent dose in the very short CHART schedule would have been around 72 Gy which should have produced a statistically significant improvement in loco-regional control relative to the 66 Gy in 2-Gy fractions used in the conventional arm of this trial. This provides a strong argument for a reduced rate of proliferation at very short times. The equivalent tumour outcome in the CHART and conventional arms of this trial suggests that accelerated proliferation kicks in at around 23 days after the start of radiotherapy, in remarkable agreement with other estimates of this quantity. This again would imply that very short intensive schedules are associated with a loss of the therapeutic ratio.

There is clearly a need for trying to synthesise the biological knowledge gained from the altered fractionation trials in a quantitative analysis. The fractionation Intergroup Merger of Patient data from Altered or Conventional Treatment (IMPACT) schedules study is an intergroup analysis of individual patient data from five randomised trials on radiotherapy fractionation in HNSCC conducted between 1980 and 1995. Individual patient data from 2566 patients participating in the EORTC 22791, EORTC 22811, EORTC 22851, the Princess Margaret Hospital (PMH) and the CHART head and neck trials have been recoded and merged into a joint database. The IMPACT project consists of several detailed studies aiming to estimate various radiobiological parameters characterising the response of head and neck carcinoma to fractionated radiotherapy.

2.2. Individualisation of fractionation schedules

Very different dose-fractionation schedules, from the strongly accelerated CHART schedule delivering 54 Gy in 36 fractions over 1.5 weeks to the EORTC 22791 hyperfractionation schedule delivering 80.5 Gy in 70 fractions over 7 weeks, have been tried against conventional fractionation in large well-conducted randomised controlled trials. Admittedly, these altered fractionation schedules have not been directly compared in a randomised controlled trial. None the less, it is remarkable that they both offer quite adequate therapy to unselected patients with locally advanced HNSCC. Using the linear quadratic model with $\alpha/\beta = 10$ Gy, the estimated difference in EQD_2, without correction for overall treatment time, is 23 Gy. It is almost inconceivable that all patients should have the same trade-off between dose and time and this raises the question: Is it possible to identify subgroups of HNSCC patients who would benefit from a specific type of altered fractionation?

Much effort has gone into the attempts to develop radiobiologically-based predictive assays for selection of

dose-fractionation schedules and many of the clinical studies have been in patients with HNSCC. Overall, these studies have failed to establish a clinically useful predictive assay [8]. Possibly, the biological basis for these assays has been oversimplified and it seems that other routes must be followed for selecting cases for specific schedules.

There are a few hints in the published reports from the altered fractionation trials that patient selection may indeed be possible. Data from the CHART and the DAHANCA studies suggest that primary tumours have a relatively greater benefit from AFX than lymph nodes. In the same two studies, there is also the suggestion that well differentiated tumours have a greater benefit than poorly differentiated tumours. Differentiation is a composite biological 'marker' and it is possible that this is only an epi-marker for some underlying phenotype. It is likely that progress in cancer biology will lead to tailored fractionation schedules in the near future (see also Section 5 below).

2.3. Early normal tissue response to altered fractionation

The dominating early normal tissue reactions after radiotherapy in the head and neck region is radiation mucositis [9–11]. In most toxicity grading systems, this reaction is scored based on the morphological changes in the appearance of the mucosa. This has been shown, however, to correlate well with functional mucositis (dysphagia) and mucosal pain [1,11] . While the weight loss previously associated with functional mucositis may be relieved through the introduction of a percutaneous gastric tube, severe mucosal reactions are still a major clinical concern due to the possible progression of these into consequential late reactions [12–14].

With quite similar radiobiological parameters characterising the mucosal and tumour response to changed overall treatment time and changed dose per fraction, it has so far not been possible to devise schedules dissociating the effect on the normal mucosa and the HNSCC. This observation has been condensed in the saying 'No pain, no gain'. There are basically two ways around this linking. The first one is to exploit the dependence of the incidence of mucosal reactions on the mucosal area irradiated [11]. This may be accomplished using 3D conformal radiotherapy or Intensity Modulated Radiotherapy (IMRT). The other way of changing the balance between tumour control and mucosal reaction is by the use radio-protectors or biological response modifiers and these strategies are briefly discussed below.

2.4. Late normal tissue morbidity

As regards the late treatment sequelae *after* accelerated fractionation, radiobiology research in the 1980s and early 1990s showed that proliferation in late-responding normal tissues was so low, that the effect of overall treatment time on the tolerance of these tissues would be minimal or even zero. Thus, it should be possible to devise accelerated fractionation schedules providing an increased tumour control probability and/or at the same time, a constant or reduced incidence of late morbidity. Indeed, two accelerated schedules, CHART [15] and TROG 9101 [16], have been associated with a significant reduction in the incidence of late normal tissue morbidity compared with conventional fractionation. This supports the principle that short intensive schedules may allow a dose reduction that is beneficial in terms of reducing treatment toxicity without compromising tumour control. However, in the case of CHART, the change in late morbidity was less than what would be expected from the linear-quadratic model assuming complete repair between dose fractions. This surprising finding may in fact be one of the most intriguing biological observations from the quite comprehensive clinical research effort in altered fractionation! An analysis shows that the CHART data may be explained by incomplete repair between one dose fraction and the next [17]. This could arise if the repair of—or more generally the *recovery* from — sublethal radiation damage between dose fractions follow mono-exponential kinetics with a half-time of some 4–5 h. This model also explains the very significant increase in the incidence of fibrosis in the AF arm of the EORTC 22851 trial and is supported by evidence from other clinical and experimental studies [17]. The clinical and biological significance of such long recovery half-times is that they put a constraint on the therapeutic gain from multiple-fractions-per-day schedules which again will ultimately define a limit for how far the rationales of HFX and AF can be pushed.

2.5. Where next in altered fractionation in HNSCC?

While the clinical radiobiology of fractionation in the definitive treatment of HNSCC is increasingly well understood, optimisation of dose fractionation has still a long way to go when radiotherapy is combined with other modalities, surgery or chemotherapy. The special aspects of postoperative therapy and radiation fractionation in radio-chemotherapy will be discussed in the relevant sections below.

A number of novel strategies for modulation of tumour response to cytotoxic therapy are in preclinical or early clinical development and a few of these will be briefly discussed below. Several classes of these, e.g. DNA repair inhibitors or growth factor antagonists, would affect the choice of optimal radiation dose fractionations.

In addition, 3D conformal radiotherapy or IMRT may improve the radiation dose distribution and thereby allow sparing of late effects without compro-

mising tumour control probability. The principle of sparing of long-term function by partial irradiation of organs at risk has been demonstrated for the parotid gland [18,19]. This again, may open a window of opportunity for novel dose fractionation schedules or even the use of varying dose fraction sizes throughout the target volume. One example of the latter is the suggested delivery of a hypofractionated simultaneous boost with IMRT [20].

3. Radio-chemotherapy combinations

The case for combining radio- and cytotoxic chemotherapy is compelling. There are at least four basic mechanisms by which the combination of the two modalities may result in a therapeutic gain (adapted from Ref. [21]):

- Spatial cooperation, i.e. the concept that radiotherapy may be effective against loco-regional disease whereas chemotherapy may be effective against (occult) systemic disease
- Additivity, whereby the two modalities act independently to increase the total cell killing
- Enhanced radiation response, whereby the chemotherapy enhances the effect of radiotherapy in a supra-additive way
- Protection of normal tissues, this effect has been observed, but as a result of stimulated proliferation of normal-tissue cells. It is doubtful whether this is a clinically useful effect in any case.

Whether a given radio-chemotherapy combination actually provides a worthwhile therapeutic gain depends on whether the improvement in tumour outcome is sufficient to outweigh the toxicity of the combination. Steel actually proposes *independent toxicities* as a fourth rationale, however, toxicity can only be meaningfully considered in the framework of an overall therapeutic gain [63].

More than 70 trials including over 12 000 patients have investigated combined loco-regional and chemotherapy as an alternative to loco-regional therapy alone. Several authors have reviewed the clinical experience on combined radio-chemotherapy (e.g. Ref. [22–27]) and at least four formal meta-analyses have been published [22,24–27]. A variety of drugs have been tried, as mono- or poly-drug chemotherapy, and a number of schemes for the sequencing of chemotherapy and radiotherapy have been studied.

3.1. Sequencing of radiation and chemotherapy

Chemotherapy may be administered as neoadjuvant, concurrent or adjuvant therapy depending on whether it is given before, during or after the course of radiotherapy. A number of possible advantages and disadvantages have been suggested for each of these sequences and some of these are summarised in Table 1. The consistent, frequently cited, message from the meta-analyses is that patients with locally advanced tumours achieve a modest, but highly statistically significant survival benefit from *concurrent chemo-radiation* (CRT) whereas *neoadjuvant* chemotherapy (NACT) and *adjuvant* chemotherapy (AdjCT) did not convey a significant survival advantage. This seems to be in agreement with the findings in other tumour types, e.g. oesophageal and cervical cancers. The more important, but generally overlooked, finding is that there is a highly significant heterogeneity in the observed treatment effect among the trials. In other words, the modest overall effect of CRT on survival is the result of pooling highly effective regimens with less effective or even detrimental regimens. It can easily be argued that the very basis assumption for performing the meta-analysis is not fulfilled. Similarly, it may be premature to discard the role of NACT and AdjCT based on the findings of the meta-analyses: as summarised in Table 1, a number of theoretical advantages are offered by these approaches and these might be translated into more marked survival benefits by the use of novel, more active drugs. These drugs, on the other hand, may be too toxic if administered concomitantly with radiotherapy.

The aim of many early trials of neo-adjuvant chemotherapy (NACT) was to improve disease-free survival. The long-term outcome of these studies showed that, at least with the drugs available in the 1980s and 1990s, this goal was not reached. What NACT *has* achieved is mainly in relation to organ preservation programmes (see below).

Most randomised controlled trials conducted in the 1980s and 1990s have investigated concurrent or neoadjuvant schedules. Adjuvant chemotherapy, at doses effective against occult metastasis, may be attractive if patients at high risk of harbouring minimal systemic disease could be reliably identified and this is briefly discussed below.

Another route of investigation relates to mixed schedules, for example the addition of CRT to NACT. Early clinical trials are needed to assess if such schedules are feasible and may yield higher response rates without causing unacceptable early and late morbidity in normal tissues. This type of combination between radiation and cytostatic agents is also investigated in non-small cell lung cancer and could theoretically represent an effective attack of the malignant process at both the primary and metastatic sites. It remains to be seen if the theoretical advantages of two types of sequencing can be exploited in a schedule designed to overcome the potential weaknesses of the elements of the mixed schedule.

Table 1
Rationales for scheduling of cytostatic drugs and radiation therapy

Scheduling	Proposed advantages/possible disadvantages	Comments
Neoadjuvant (NACT)	Advantages?	
	Short delay between referral and onset of active therapy	While this may seem attractive to patients and doctors, the apparent benefit may be offset by the induction of accelerated proliferation.
	Induces shrinkage of the macroscopic tumour in a high proportion of all cases leading to a possible reduction in irradiated volume	In HNSCC, the risk of geographical misses counteracts a major RT target volume reduction. However, it has been shown that more conservative surgery may be possible after NACT [55].
	Tumour shrinkage may cause re-oxygenation	This has been shown in xenografts [56]. It may potentially be of special interest in patients with oral cavity carcinoma treated with intra-arterial infusion CT [57].
	Allows clinical response to CT to be assessed which may reliably predict RT response	This would in principle allow individualisation of the subsequent therapy—however, this has not been shown in practice to improve outcome.
	Offering possibilities for a larger range of therapeutic targets for CT and RT	Some drugs, e.g. gemcitabine, taxanes and anthracyclines, have strong interactions with RT when given concurrently.
	Allows CT scheduling and doses that are effective against micro-metastases	Long-term follow-up suggest a reduction in DM incidence following NACT with a minimum of three courses of CT.
	Disadvantages?	
	CT may induce accelerated repopulation	This may explain the lack of an improvement in loco-regional control with neoadjuvant CT + RT due to the often very long interval between the start of CT and end of RT.
	Might reduce compliance to subsequent therapy	This has been suggested for example in a randomised phase II trial in nasopharyngeal cancer patients [58].
	Clonal selection of radioresistant cells	May explain the lack of an improved loco-regional control with NACT.
Concurrent (CRT)	Advantages?	
	No protraction of the overall treatment time relative to RT alone	Unplanned treatment interruptions due to early morbidity may be a concern. Overall treatment in alternating schedules might be increased.
	Some drugs may act as radiosensitisers and therefore also improve loco-regional control	This is consistent with the observed marked increase of loco-regional control from CRT. However, exact biological mechanism unknown.
	RT may improve drug uptake	Has been demonstrated *in vitro* for carboplatin [59] and 5-FU [60]. Has been exploited clinically for break-down of the blood–brain barrier—unclear, if this mechanism is clinically relevant in HNSCC.
	Disadvantages?	
	Increased toxicity due to interactions between CT and RT	Early toxicity is generally increased; this may preclude the use of certain types of drugs and/or necessitate drastic dose reductions; radio- and/or chemoprotective drugs may play a role here. Late toxicity assessment requires longer follow-up than what has typically been available in studies published so far. High conformality RT may reduce this problem.
	May be necessary to reduce intensity of CT or RT (or both) especially at cytostatic dose levels	This could potentially reduce the efficacy against micro-metastases. However, the incidence of distant relapse has been found to be reduced after CRT in several studies.
Adjuvant (AdjCT)	Advantages?	
	CT is given after the tumour burden is reduced	This could potentially improve drug delivery.
	Allows a CT dose that is effective against micro-metastases	A reduction of DM incidence has not been shown for AdjCT in HNSCC. Might be relevant in DM high-risk patients, e.g. locally advanced nasopharyngeal carcinoma.
	Disadvantages?	
	Long time interval before the start of CT	This might in particular be a problem if homeostatic control made occult metastasis accelerate their proliferation after primary tumour debulking.
	RT may select for chemo-resistant clones	This might explain the lack of significant improvement in loco-regional control.
	Offering possibilities for a larger range of therapeutic targets for CT and RT	Some drugs, e.g. gemcitabine, taxanes and anthracyclines, have strong interactions with RT when given concurrently.
	Reduced access of drug to tumour bed due to fibrosis and vasculature impairment after RT	This mechanism has not been directly shown in the clinic.
	Tolerance to CT may be compromised by the preceding RT	This explains the poor compliance observed in many studies

CT, chemotherapy; RT, radiotherapy; HNSCC, head and neck squamous cell carcinoma; 5-FU, 5-fluorouracil; DM, distant metastases.

The considerable toxicity experienced with the radio-chemotherapy regimens applied so far motivates research into biological response modifiers. Such agents might increase tumour response, but with fewer normal tissue sequelae than schedules increasing the radiation or cytostatic drug dose intensity.

3.2. Which drugs should be used?

In the 1980s and 1990s, the drugs of choice in CRT were mitomycin-C, cisplatin, and 5-fluorouracil (5-FU) and these were selected based on both *in vitro* and *in vivo* experiments. Cisplatin was found to yield the largest enhancement in cell killing, whilst mitomycin-C was shown to selectively kill hypoxic cells. As a consequence, these drugs have been extensively investigated in phase III trials, for all types of radio- and chemotherapy scheduling (Table 1). It seems reasonable to assume that the therapeutic potential of these drugs have been taken to their limit.

The comprehensive meta-analysis by Browman and colleagues [24] analysed the mortality odds ratio according to the type of drug (Fig. 2). Platinum and mitomycin C-based regimens were associated with an odds ratio significantly lower than 1 whereas this was not the case with bleomycin- and 5-FU-based regimens. Note, however, that the effect of the two latter drugs is actually not statistically significantly different from the effect of platinum- and mitomycin-C-based regimens. The authors also estimated the odds ratios for single and multi agent regimens and, again, there was no difference.

Despite their proven effectiveness, the associated enhancement of both acute and late reactions, such as acute mucositis with 5-FU or skin fibrosis with cisplatin, and the fact that only sub-optimal drug concentrations are often achieved in tumour tissues present a strong case for the design and clinical testing of new drugs in the radio-chemotherapy of HNSCC.

Phase I-II studies have recently been activated to test the feasibility and effectiveness of new drugs like taxanes, topoisomerase I inhibitors and nucleoside analogues (fludarabine and gemicitabine), which might be more potent in affecting postradiotherapeutic DNA damage and repair inhibition. Further improvements in the therapeutic index could possibly be obtained by a rational selection of drugs based on their intrinsic cytotoxic mechanisms and their interaction with pathways leading to radiation-induced cell death.

Optimisation of the therapeutic index means to take advantage of biological properties that differ between tumour and normal tissue cells. There are at least four major avenues to explore in preclinical and clinical research. The first one is to select drugs able to overcome independent mechanisms of cross-resistance with radiation therapy. An example is the combination of radiation with drugs, e.g. camptothecin, with preferential activity against cells in the relatively radioresistant S-phase [28]. The second avenue is to develop strategies for the selective inhibition of tumour cell repopulation during radiotherapy compared with the dose-limiting normal tissues. Here, current interest focuses on targeting the epidermal grow factor (EGF) receptor either by monoclonal antibodies like C225 (cetuximab) or tyrosine-kinase inhibitors, e.g. ZD1839 (Iressa, Astra Zeneca) now in phase I trial in patients with HNSCC receiving radiotherapy with or without cisplatin (NCI-4551). ZD1839 has been shown in skin biopsies from patients participating in phase I trials to inhibit EGFR activation and affect downstream receptor-dependent processes [29] and is also currently being tested as a single-agent therapy in recurrent or metastatic HNSCC in a phase II trial (NCI-1701). Cetuximab is now being tested with conventional or

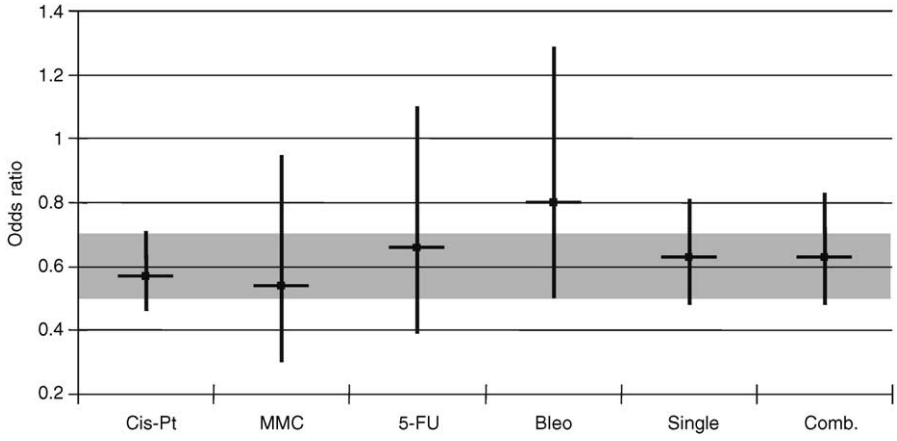

Fig. 2. Odds ratios (with 95% confidence limits) of mortality after CRT versus radiotherapy alone for various types of chemotherapy: Cis-pt, platinum-based; MMC, mitomycin C-based; 5-FU; 5-fluorouracil-based; Bleo, bleomycin-based; Single, single-agent chemotherapy; Comb, multi-agent chemotherapy. The grey shaded band corresponds to the 95% confidence interval for all data combined. Data from Browman and colleagues [24].

accelerated radiotherapy in locally advanced HNSCC in a phase III trial in the USA (NCI-G99-1657) with a target accrual of 416 patients. The third strategy aims to attack the problem of hypoxic cell radioresistance. This may be achieved through the use of drugs with selective toxicity to hypoxic radio-resistant tumour cells. An example is tirapazamine, which showed promising results in a phase I trial when combined with concurrent cisplatin and radiotherapy. In addition, vascular targeting agents such as 5,6-dimethylxanthenone-4-acetic acid (DMXAA) [30] and combretastatin [31] may be used in combination with radiation. Erythropoietin in HNSCC patients with a low haemoglobin concentration is currently being tested in phase III trials by the Radiation Therapy Oncology Group (RTOG) (trial 9903) and the EORTC (trial 22996-24002). The fourth avenue is a mixed bag of strategies springing from our improved understanding of tumour biology: aiming at inducing apoptosis, modulating signalling pathways or inhibiting angiogenesis [32].

Finally, there is still an interest in normal-tissue radio-protectors such as amifostine. This compound is currently tested in randomised phase II trials, e.g. in the EORTC 24981 trial of CRT for locally advanced nasopharyngeal carcinoma after NACT. The crucial question here, of course, is whether these compounds can provide selective protection of the normal tissues [33].

3.3. What radiotherapy should be used?

Most radio-chemotherapy trials have employed conventional radiation fractionation schedules and the clinical evidence to allow a comparison between various strategies is sparse. A recent study [34] was interpreted as support for the hypothesis that the relative importance of adding chemotherapy was reduced with an accelerated radiotherapy schedule. Yet, a more detailed analysis showed that the magnitude of the effect seen in the study was entirely consistent with the estimates from the meta-analyses [35].

What is clear, however, is that combining the best available radiotherapy fractionation schedule with chemotherapy may not necessarily optimise treatment outcome. Furthermore, combined modality therapy may change the desirable radiation dose distribution both with respect to normal-tissue constraints and the dose in the clinical target volume. Throughout the last decades, considerable efforts have been made by many physician and physicist teams to develop and validate various techniques of computed tomography (CT)-guided three-dimensional conformal radiotherapy planning. Again, IMRT allows a specific optimisation of the radiation dose distribution which, at least in principle, could be modified according to the specific risk of morbidity from a given radio-chemotherapy schedule.

3.4. Organ preservation

Perhaps the most important application so far of NACT has been in programmes of organ preservation. Trials conducted in the 1980s and 1990s in patients with laryngeal–hypopharyngeal carcinomas amenable to surgery, such as the Veterans Affairs Cooperative Laryngeal Cancer Study Group [36] and the EORTC 24891 trials [37], used the most active drugs available then, cisplatin and 5-FU. These trials showed that: (a) the incidence of treatment failures at local, regional and second primary sites was roughly the same in the immediate surgery and the NACT arms; (b) there were a lower incidence of distant failure in the NACT arm than in the surgery-alone arm; (c) the observed hazard ratios for disease-free survival indicated that the two treatments were equivalent, but approximately one-third of the patients assigned to the NACT arm were given the possibility of retaining a functional larynx.

An important question is to optimise the type of NACT for organ preservation programmes. A comparison between NACT and alternating radio-chemotherapy based on cisplatin and 5-FU will come from the EORTC Trial 24954, which will be closed for accrual in early 2003. Other important research priorities in the next 5 years are:

- Testing the impact of new agents, cytotoxic and others, on tumour response to radiation
- Comparing novel NACT with CRT regimes
- Testing the effectiveness of normal tissue radioprotectors
- Establishing the role of Intensity Modulated Radiation Therapy (IMRT) and new fractionation schedules on treatment outcome.

3.5. Chemoprevention

HNSCC is thought to progress from a premalignant to a malignant lesion through multiple genetic alterations. This model is consistent with the high incidence of second primaries after successful treatment of a head and neck cancer. Chemoprevention in HNSCC may be seen as a special case of adjuvant drug therapy. Prospective clinical phase III trials in large cohorts of curatively treated early stage HNSCC, like EUROSCAN [38] in oral and laryngeal cancer, failed to demonstrate a significant reduction in the incidence of second primary cancers or loco-regional recurrences. It may be argued, however, that the previous prospective studies were conducted in patient populations characterised by a high heterogeneity in risk factors and lifestyles. Future chemoprevention trials should probably concentrate on those early-stage patients who stop

smoking at the time of primary diagnosis. Heavy smoking during and after the primary treatment are likely to have confounded the putative effect of chemopreventive compounds.

4. The postoperative setting: a special entity where treatment is still to be optimised

Adding surgery to the management of locally advanced HNSCC adds a multitude of therapeutic possibilities, but also raises a number of unresolved clinico-biological questions.

4.1. Post-operative radiotherapy alone

There are reasons to assume that accelerated proliferation of any remaining tumour cells may be triggered by the surgery. These are partly the observation from un-controlled clinical studies of a marked influence of the interval between surgery and radiotherapy on prognosis and partly biological arguments relating to release of cytokines and growth factors in the surgical scar and (hypothetical) homeostatic control mechanisms. Phase III trials [39,40] have demonstrated a major advantage of accelerated fractionation of postoperative radiotherapy. If accelerated proliferation starts after a 3-week delay, but the 3 weeks should be counted from the time of surgery, then this would mean that very short schedules could be advantageous in this setting. This is consistent with the data from Awwad and colleagues [40] and forms the rationale behind the postoperative HNSCC trial of CHART weekend less (CHARTWEL) versus conventional radiotherapy conducted by the Medical Research Council in the UK.

4.2. Postoperative chemo-radiotherapy

Introducing chemotherapy in the postoperative management of high-risk patients is a logical extrapolation of the experience with chemo-radiotherapy as a definitive treatment for HNSCC. In addition, in this case the optimal schedule remains to be clarified. Early results are available from the EORTC 22931 trial [41] and the RTOG 9501 trial [42]. The designs of these trials are quite similar. The EORTC trial investigated the efficacy of CRT as postoperative therapy for patients presenting with carcinoma of the oral cavity, oropharynx, hypopharynx or larynx, T3-4, any N, M0 or T1-2, N2-3, M0 or T1-2, $N<2$ and high risk factors: insufficient resection margin, peri-neural involvement, vascular embolisms or extracapsular spread. From 1994 to October 2000, 334 patients were randomly assigned to either radiotherapy alone, up to 66 Gy in 33 fractions, or CRT, using the same radiotherapy schedule, but combined with three courses of cisplatin, 100 mg/m^2 on days 1, 22 and 43. Early results have been analysed with a median follow-up of 34 months. Disease-free rate was the primary endpoint for efficacy and the 3-year estimates were 41 versus 59% in favour of the experimental arm ($P=0.010$). Significant differences were also found for loco-regional control (64 versus 83%, $P=0.0014$) and for overall survival (49 versus 65%, $P=0.006$). The follow-up is still too short to evaluate distant metastasis rates and late effects in normal tissues.

The RTOG 9501 inclusion criteria were the following: two or more involved lymph nodes, presence of extracapsular effraction in neck nodes, or microscopically involved mucosal margins. Thus, all patients included in the RTOG study had pathologically positive neck nodes (pN+), whereas approximately a quarter (23%) of the cases randomised in the EORTC trial were pN0. There were also approximately twice as many oropharyngeal carcinomas in the RTOG study as in the EORTC trial.

The RTOG trial randomised a total of 459 patients, and preliminary results were reported at a median follow-up of 26.6 months. The RTOG study also showed a trend towards improved outcome in the CRT arm, but the P values were less significant [42]. Whilst there was a significant difference in 2-year disease-free survival in favour of the CRT arm (42 versus 54%, $P=0.049$), the loco-regional control and overall survival rates were only marginally improved (74 versus 79%, $P=0.16$ and 57 versus 63%, $P=0.51$, respectively). In this trial, both severe acute and late toxicities were significantly increased in the CRT arm ($P<0.0001$).

No obvious explanation can be found so far for these differences in the magnitude of the benefit from postoperative CRT in the RTOG and the EORTC trials. The difference in patient population may be relevant, although this would need a more detailed analysis when the data are mature. Both trials have a rather short follow-up and a more precise assessment of the value of postoperative CRT in high-risk HNSCC will have to wait, especially with regard to the incidence of late normal-tissue morbidity and assessment of the therapeutic index of CRT. Further treatment intensification using more effective drugs or altered radiation fractionation in very-high-risk patients should be considered once the therapeutic index of the current regimen is established.

5. Tailoring therapy to the individual patient

As discussed briefly above, research into radiobiological predictive assays has so far failed to develop a clinically useful assay. This does not imply, however, that patient selection for a specific type of therapy would not be achievable by means of novel assays. It is beyond the scope of the present paper to review this exciting field, but a few examples will be given to provide an impression of the direction of current research.

Roughly a third of HNSCC patients with clinically negative neck nodes will eventually experience nodal failure and several centres have studied the feasibility and sensitivity of sentinel node biopsies for staging of a clinically negative neck in HNSCC. The overall experience from more than 300 cases was that the sentinel node could be identified in 95% of these and that the sensitivity of the method is similar to that of a staging neck dissection [43].

Several imaging modalities, including 18F-FDG positron emission tomography (PET), X-ray CT, magnetic resonance imaging and ultrasound, have been investigated and compared with postoperative staging [44]. While PET had the highest specificity and ultrasound the highest sensitivity, none of these methods had a diagnostic accuracy exceeding 76%.

Although loco-regional disease progression remains the dominant type of treatment failure in HNSCC, distant metastases are a significant clinical problem as well. This is likely to become even more of a problem as the success of loco-regional therapy increases. The very sensitive reverse transcriptase-polymerase chain reaction (RT-PCR) assays have been evaluated for the detection of mRNA transcribed from epithelial genes in bone marrow, blood or lymph nodes [45,46]. This method is promising for identifying patients with minimal systemic disease at the time of diagnosis.

Due to the spatial cooperation of radiotherapy and systemic therapy, and the fact that both add to the overall toxicity of therapy, it would be valuable to develop prognostic indices for specific failure types. An example was recently published using competing risks methodology to identify prognostic factors for distant and loco-regional relapse after radiotherapy for non-small cell lung cancer [47]. A number of immunohistochemical markers have been assessed in HNSCC biopsies from patients included in the CHART randomised controlled trial [48]. Currently, a competing risks analysis is in progress with the aim of estimating individual risk profiles for failure in T, N and M.

With the advent of high-throughput biological assays, tissue microarrays and cDNA microarrays, individual patient risk profiling is likely to be refined to an extent that it will provide a clinically useful guidance for therapy optimisation.

6. Conclusion

With an increasing number of new strategies being developed and going into clinical trial, careful recording and documentation of normal tissue morbidity becomes a key factor in treatment optimisation [49,50]. Much of the evidence gained in the 1980s and 1990s relates to tumour outcome, but is rather weak when it comes to treatment-related morbidity and quality of life. The morbidity after intensive combined modality therapy is considerable and this must be a research priority if further progress is to be made. It is necessary to optimise the therapeutic ratio Again, radiobiological predictive assays have been developed for normal tissue effects after radiotherapy [51], but so far without a useful clinical assay emerging. Nevertheless, a recent study [52] estimated that more than 80% of the variability in the expression of skin telangiectasia after radiotherapy was deterministic rather than stochastic which is obviously encouraging in terms of trying to predict and modify this normal tissue reaction. Finally, it should be mentioned that a number of interesting strategies are in preclinical or early clinical development for modifying the induction or processing of radiation injury in normal tissues. A concise overview of this exciting field has been presented recently by Stone and colleagues [53].

From the experiences of the last decade, it appears that translational and clinical research in HNSCC in the coming years will follow multiple avenues: (a) clinical evaluation of novel cytostatic drugs; (b) development of targeted non-cytotoxic drugs; (c) optimisation of multimodality therapy as a 'package deal'; (d) development of new organ preservation programmes, as a result of either an increase in dose intensity of the current CRT regimes or combining these with NACT; (e) research in genomics, proteomics and bio-imaging with the aim to tailor therapy to the individual patient; (f) exploring the progress in radiotherapy planning and delivery, in particular intensity modulated radiotherapy; (g) research on strategies for ameliorating or treating treatment-related morbidity; (h) research on chemo-prevention of second primaries in early stage cancer patients.

All of these challenges will require a major investment in translational research and in evidence-based oncology [54]. With an increasing refinement of indications for and choice of therapeutic strategy, large collaborative research groups and even intergroup studies will be needed to allow sufficient numbers of patients to be accrued over a reasonable period of time. Last, but not least, campaigns for prevention—in terms of changing the life-style of high-risk populations—and early diagnosis of these diseases have to be promoted in order to reduce the need for aggressive therapeutic approaches.

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