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Chemoradiation schedules—what radiotherapy?

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Abstract

Synchronous chemoradiation (SCRT) is playing an increasing role in the primary and multimodality management of cancer in many disease sites. Current schedules have been in the main empirically derived, and the addition of chemotherapy has in some cases led to a compromise in the total dose or scheduling of radiotherapy. Non-randomised phase II studies abound, but there are few well designed phase III randomised studies with comprehensive acute toxicity data and mature follow-up. In many sites long-term survival is unusual. So severe morbidity and long term functional outcome is poorly documented. It is therefore difficult to assess the real benefit of SCRT. This review uses the endpoints of local control and overall survival from randomised trials in small and non-small cell lung cancer, head and neck cancer, oesophageal cancer, rectal and anal cancer. We explore the evidence for total dose; fractionation; fraction size; the effects of a gap in treatment; and scheduling of radiation in SCRT.

Conclusions: An optimal schedule of SCRT has not yet been derived. The enhanced acute toxicity and persistent high risk of local failure in many disease settings with current SCRT schedules demand that more effective and less toxic treatment strategies must be identified in the future. These schedules should be tested in randomised trials with the emphasis on meticulous reporting of acute toxicity endpoint and documenting the field sizes or proportions of critical organs within the high dose area if we are to derive the optimal therapeutic ratio.

Keywords: Chemoradiation; Radiation therapy; Chemotherapy; Cancer; Dose; Fractionation

1. Introduction

Not all localised cancers can be controlled by radiation alone. In general, larger more advanced cancers are more difficult to control than smaller ones. By the time a cancer has progressed to a locally advanced status, e.g. lung cancer stage IIIa or IIIb or a T4 oesophageal or T4 rectal cancer, the likelihood of radiotherapy alone to achieve local control is low. In addition, patients with more advanced tumours are also much more at risk of developing metastases. The concept of synchronous chemoradiation (SCRT) is therefore attractive, as it combines a systemic chemotherapy treatment together with an interaction within the radiation portals.

Explanations of why radiation alone fails to achieve local control have been ascribed to intrinsic radio-resistance, hypoxic cell resistance and repopulation as a result of increasing cell proliferation. To some extent, these mechanisms can be, and have been, overcome by either increasing the total dose of radiotherapy or employing schedules of hyperfractionation with acceleration or concomitant boost techniques. Improvements in the techniques of radiation such as intensity-modulated radiotherapy (IMRT) and conformal therapy have also enhanced the therapeutic ratio and allowed the delivery of higher doses. These strategies of intensifying the radiotherapy have been moderately successful when radiotherapy has been used alone, but are they the most logical strategies to integrate in SCRT with synchronous chemotherapy?

There is no consensus concerning what is the standard or optimal dose of radiotherapy when combined with chemotherapy. Historically, developments in chemoradiation have been based on the premise that preoperative treatment, either radiotherapy or chemotherapy, could effectively downstage a primary tumour and either increase complete resection rates or provide scope for organ-sparing procedures, as in head and neck cancer. Clinicians originally appear to have been cautious in terms of the total dose of radiotherapy—

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particularly in the context of preoperative SCRT. An early pioneer, Norman Nigro used a short course of low-dose radiotherapy (30 Gy in standard fractionation of 2.0 Gy) concurrently with the chemotherapy agents, 5-fluorouracil (5-FU) and mitomycin-C in patients with anal cancer [1]. With time, stepwise increments in the radiotherapy dose have been achieved with the growing confidence that this approach can be delivered within normal tissue tolerance.

2. Aims of the review

This review sets out to examine what has been learned concerning the role of radiotherapy within SCRT schedules, and how radiation may be exploited to its optimum. There is a plethora of non-randomised phase II studies of SCRT. When pitted against historical controls using radiotherapy alone, these studies can rarely ensure any true comparability between the two groups and should therefore be considered invalid evidence of efficacy. We will therefore concentrate on the evidence from randomised controlled trials of SCRT.

The review aims to cover the following five main topics:

1. The optimal total dose of radiotherapy in chemoradiation schedules
2. The optimal fractionation regimen
3. The ideal fraction size
4. The effects of a gap in the middle of SCRT
5. The ideal scheduling of the radiation component

3. Materials and methods

A literature search was performed using Medline and Cancerlit over the period 1996–2001 supplemented by hand searching of abstracts from the Proceedings of the American Society of Clinical Oncology (ASCO) meetings. Several keywords have been used which include synchronous, concurrent, chemoradiation, chemoradiotherapy with a particular emphasis on head and neck cancer, non-small cell lung cancer (NSCLC), small-cell lung cancer (SCLC), oesophageal cancer, anal and rectal cancer. There remain distinct methodological problems in comparing the evidence from some of these studies which we will discuss.

3.1. Problems in interpretation of available data

Interpretation of randomised controlled trials of SCRT is problematic. Older studies rely on primitive imaging and unsophisticated methods of planning and delivery of radiation and the delivered dose is difficult to extrapolate. Few studies have been published with updated long-term follow-up and survival data [2]. Most trials have demonstrated an increase in acute morbidity of SCRT when compared with the same radiation dose or schedule in the control arm. Thus, any increase in overall or disease-free survival has usually been achieved at the expense of exaggerated local reactions [3]. In cancer of the oropharynx, 5-FU- and carboplatin-based SCRT showed a trend to an improved survival, but substantially increased toxicity in terms of acute mucositis—often resulting in marked weight loss and even a requirement for tube feeding [4]. Sadly, many trials continue to report results without adequate information regarding toxicity.

Although SCRT is associated with increased levels of acute toxicity, this does not always lead to an increase in late radiation morbidity [4,5]. SCRT in oesophageal cancer can lead to severe late fibrosis associated with poor swallowing [6]. A German study of hyperfractionation using SCRT has reported that 19 of 64 long-term survivors (30%) of a head and neck study remain dependent on tube feeding [7]. Significantly more patients had persistent swallowing problems in the SCRT arm (51% versus 25%).

Even with hyperfractionated radiotherapy in a concurrent schedule with cisplatin, one study in oesophageal cancer found that 11% of patients experienced grade 3 late oesophageal toxicity [8].

The long-term late toxicity of these regimens (oedema, fibrosis, necrosis and functional swallowing) may not be fully appreciated until at least 5–10 years have elapsed following the completion of treatment. Late morbidity is therefore almost certainly underreported, partly because in many disease sites there are so few long-term survivors.

A further consistent problem is the finding that the incidence of non-malignant and intercurrent deaths is often higher in the SCRT arm of randomised trials [9–11]. Again, many trials do not offer sufficient information to judge the scale of this phenomenon.

Although there is some evidence that SCRT leads to better local control, significant improvements in disease-free and/or overall survival have proved more elusive. Few studies of SCRT, therefore, have definitively confirmed a therapeutic advantage. There are many sceptical radiation oncologists who continue to argue that, although the addition of chemotherapy can produce some gains, these gains are only achieved at considerable cost in terms of exacerbated acute local radiation reactions and could have been achieved just as effectively by increasing the dose of radiotherapy [12].

In retrospect, many of the randomised trials have indeed compared SCRT against an inadequate/suboptimal dose of radiotherapy. Many trials even have included a split course or gap in the radiotherapy. For this reason, in some trials there appears to be a spurious advantage to SCRT which might evaporate given

optimal doses/schedules of radiotherapy in the control arm.

Only a few trials have compared lower-dose radiation in the context of SCRT against maximal/optimal doses of radiotherapy alone. The best known such trial [3] was performed in oesophageal cancer and compared 50 Gy plus 5-FU/cisplatin during the first and the last week, followed by two courses of 5-FU/cisplatin against the higher (and probably optimal for the volume of tissue irradiated) dose of radiation alone (64 Gy) in the control arm. Survival was 10% at 2 years for radiation alone compared with 38% in the combined SCRT arm. More mature follow-up [2,13] confirmed a significant survival advantage for SCRT. In the radiotherapy alone arm, there were no 5-year survivors; in the SCRT arm, the 5-year survival was 28%. This trial with mature follow-up is in stark contrast to the vast majority of published trials concerning SCRT which really do not allow conclusions to be drawn about the long-term advantage of the addition of chemotherapy to standard treatment.

If the majority of trials have very short follow-up and sparse late toxicity data, what are the end-points we could use to compare the results in each anatomical site? Additional difficulties arise because some trials are performed in a multimodality setting. How do we assess local control when surgery is a major component of the treatment in one arm and not the other? The endpoint of local control can be blurred by many factors. Persisting masses at the completion of treatment have rarely been subjected to biopsy. In some studies, only a first event was counted and follow-up in some studies was lamentably short—all of which will tend to overestimate the efficacy of treatment. Definitions of local control also vary and do not allow comparison between different trials.

So what end-points can be considered for valid, useful and effective trial comparisons?

1. Local control?
2. Five-year survival rates?
3. Event-free survival?
4. Surrogate end-points such as R0 resections, complete pathological response or downstaging the primary tumour and the nodal status?
5. Overall treatment toxicity, e.g. surgical complications and acute and intermediate severe toxicity in order to analyse the feasibility and safety of SCRT and how this can be transcribed to the multicentre setting?
6. Organ-sparing or functional end-points, particularly in head and neck cancer, rectal cancer and in bladder cancer?
7. How do we integrate late functional and quality of life issues into the overall assessment of an optimal radiation regimen?

Long follow-up is essential if the functional quality of life issues are to be used. In contrast, the surrogate end-points can be assessed at an earlier stage. Future trials will need to employ agreed quality assurance systems so that surgery, radiotherapy and histopathological reporting are comparable.

Since both treatment response and local control appear to be consistent predictors of long-term survival [14,15], some researchers have recently advocated surrogate end-points (PET scan uptake, etc.) to be integrated into current trials.

We have therefore used the end-points of local control and overall survival as indicators of treatment outcome to base comparisons between trials. Overall survival remains the most appropriate end-point, i.e. death irrespective of cause, and includes death from acute and late toxicity. Late toxicity is addressed, but few trials have sufficient follow-up and rarely use actuarial methods to correct for censoring.

We have elected not to embark on comparisons of postoperative chemoradiation as the end-points are more difficult to assess. The confounding factors of surgery, differences in the definitions of local recurrence, different practices in terms of follow-up and post-treatment scanning, and the lack of quality assurance in the pathological reporting continue to render many such trials difficult to compare and interpret.

4. What is the current accepted radiation dose in preoperative neoadjuvant chemoradiation?

Norman Nigro's intriguing early results [1] of preoperative SCRT with 30 Gy in anal cancer prompted investigators to test this novel approach in other cancers. Many have accepted complete pathological response in surgically-resected specimens as a useful and relevant end-point.

Preoperative SCRT uses lower total doses of radiation when combined with chemotherapy if the operative morbidity and mortality is to remain tolerable. Doses of radiation in these studies have typically been in the range 40–45 Gy at 1.8 Gy per fraction or even less but, in general, have led to more marked overall toxicity and higher surgical morbidity. Surgical salvage can be safely performed in head and neck cancer after chemotherapy alone, but after SCRT, surgery is associated with higher complication rates.

Early studies of preoperative SCRT in oesophageal cancer [16–18] produced complete pathological response rates (in the range of 20–30%)—much higher than those associated with either radiotherapy or chemotherapy alone. Three randomised trials compared SCRT preoperatively to surgery alone [19–21]. Both the Walsh and Urba studies [20,21] used unusual fractionation regimes with a short overall treatment time, namely 40

Gy in 15 fractions over 21 days and 45 Gy in 30 fractions over 19 days, respectively. The remaining study [19] employed a more conventional 40 Gy in 20 fractions over 28 days. All studies used 5-FU- and cisplatin-based chemotherapy. Both the Urba and Walsh studies [20,21] have demonstrated an apparent improvement in overall survival for preoperative SCRT.

A recent literature review in oesophageal cancer examined the pooled results of 52 randomised trials [22]. A total of 3078 patients received preoperative SCRT, 2315 (75%) of these underwent a surgical resection and 710 (23%) achieved a pathological complete response at surgery. Despite significant heterogeneity of radiotherapy dose, fractionation and duration and the types of chemotherapy in all these different trials, the figure of 23% for complete pathological response rate after preoperative SCRT remains remarkably standard.

In a previous meta-analysis, the same group [23] used published data from preoperative chemoradiation trials in oesophageal cancer to derive a mathematical model to predict the chance of obtaining a complete pathological response at surgery after preoperative SCRT. The model analysed both total radiation dose and dose per fraction, as well as chemotherapy dose and intensity. The repopulation factor, i.e. the radiation dose loss per day of the overall treatment time for SCRT in oesophageal cancer, is estimated at 0.83 Gy. The model suggests that increasing the total radiation dose would improve the probability of achieving a complete pathological response following preoperative SCRT. In addition, the overall duration of radiotherapy was also found to be a significant factor for improving the likelihood of a complete pathological response. The model did not take into account toxicity or survival, and ignores the possibility that overall survival could be compromised by excess acute toxicity from higher radiation doses.

Preoperative SCRT has been used extensively in locally advanced T3 and T4 rectal cancer. Three phase III trials randomised preoperative versus postoperative SCRT. The German CAO/ARO/AI094 trial, the Intergroup trial and the National Surgical Adjuvant Breast and Bowel Project (NSABP) R-03 trial. The two American studies failed because of poor recruitment and have not yet been published fully [24], and nor has the recently completed German trial with a similar design. In addition, a European European Organization for Research and Treatment of Cancer (EORTC) study which randomises between preoperative radiotherapy and SCRT, to the same radiation dose, continues to slowly accrue patients aiming for a total of 900 patients. All the above studies are mindful of the risks of late complications from pelvic radiotherapy and use conventional fractionation of 1.8 Gy per day to a total dose of 45–50.4 Gy. Using data from phase II and phase III studies, there is no obvious radiation dose response in SCRT studies for rectal cancer.

The largest study of preoperative SCRT in NSCLC was reported in 1995 as the mature results of the South West Oncology Group (SWOG) 8805 study on 126 patients with pathologically-confirmed stage III disease. Two courses of etoposide and cisplatin concurrently with a total dose of 45 Gy in 25 fractions over 5 weeks were followed by surgical resection. At entry, 60% were defined as stage IIIA (N2) and 40% stage IIIB (N3 or T4). Five-year survival was over 20% for both patients with IIIA and IIIB. A modest total dose of radiotherapy of 45 Gy is confirmed to be highly active in NSCLC as major pathological responses were observed in 60% of the cases. The pathological complete response rate was documented as 21% and a further 37% had only microscopic foci of disease [25].

Many trials in different disease sites demonstrate that complete pathological response correlates well with long-term survival. The most potent predictor of long-term survival in multivariate analysis was the eradication of N2 disease. The Intergroup trial of 111 patients with a Pancoast tumour (stage T3/T4 N0 N1) used the SWOG regimen of etoposide, cisplatin and radiotherapy (45 Gy in 25 daily fractions) prior to surgery. A pathological complete response was seen in 65% of cases. The 2-year disease free and overall survival was 55 and 70% for patients who underwent a complete resection [26].

The role of surgery following SCRT in patients with stage IIIA (N2 NSCLC) is being further examined in the current US Intergroup Int 0139 Trial. Patients are randomised between preoperative concurrent cisplatin with radiotherapy to a dose of 45 Gy followed by surgery. The novel arm has the same chemotherapy, but delivers a higher total radiotherapy dose of 60 Gy. This Intergroup trial is accruing and may help to answer the question of the optimal dose of radiotherapy for preoperative neo-adjuvant chemoradiation in NSCLC.

Until this trial reports, there is no evidence to support a radiation dose in excess of 45 Gy as a standard for preoperative SCRT in NSCLC, oesophageal cancer or rectal cancer.

5. Evidence for optimal radiotherapy in SCRT

5.1. Optimal total dose

Standard radiotherapy in most disease sites employs doses of 60–70 Gy depending on field sizes and the normal tissues within the target volume. There is an inverse relationship between tolerance dose and the volume of tissue to be irradiated. Conventionally fractionated doses of 60–66 Gy appear to be the maximum tolerated dose (MTD) in NSCLC if large fields are

employed. Attempts have been made to increase the total dose in sequential trials of radiotherapy in head and neck cancer and NSCLC. In part, this reflects the fact that advances in imaging have improved the localisation of the cancer in terms of accuracy and precision. It has thus become easier and more feasible to treat smaller volumes with a higher dose. Historical studies tended to have a poorer technique, larger volumes and lower total doses and often were associated with greater morbidity.

Dose–response curves in NSCLC have been suggested for conventionally fractionated radiotherapy. However, it is arguable whether the shape of the curve for SCRT is the same as that which applies to radiation alone. From the literature, there is little evidence to suggest that dose escalation improves survival.

The original radiation dose with SCRT employed by Norman Nigro in anal cancer was only 30 Gy [1[]. The three randomised trials of SCRT in anal cancer to date have used a first phase of radiation which varies the dose from 45 to 55 Gy without obvious demonstrable improvement in outcome for the higher doses [10,27,28].

Many preoperative SCRT schedules in oesophageal cancer in the range of 30–55 Gy can be found in the literature with similar efficacy producing a complete pathological response rate in the region of 25% [22]. Similar results have been achieved with only 45 Gy in NSCLC [25] and rectal cancer [29,30].

The mathematical model of Geh and colleagues [23] suggests that increasing the total radiation dose and maintaining the same dose of chemotherapy should offer a higher potential for achieving a complete pathological response following chemoradiation. Treatment volume has major implications for the MTD because of the dose-limiting effects of normal tissues. For this reason, randomised trials in NSCLC and head and neck cancer suggest that conventionally fractionated doses between 64 and 70 Gy can be integrated into SCRT schedules. However, there is no accepted gold standard radiation dose/schedule for SCRT in head and neck cancer. Hyperfractionated radiotherapy to doses in the region of 75 Gy remains the subject of clinical trials and should not be considered standard therapy.

A phase I study with an innovative design set out to define the MTD of radiotherapy in patients with SCLC in both a hyperfractionated/accelerated (HA) regimen and standard once-daily radiotherapy [31]. The chemotherapy was standardised as cisplatin 33 mg/m^3 days 1–3, cyclophosphamide 500 mg/m^2 on day 1 and etoposide 80 mg/m^2 days 1, 2 and 3 (PCE) for three cycles. Two further cycles of cisplatin and etoposide at the same (systemically active) doses were delivered concurrently with the thoracic radiation.

The total dose and or fraction size of the HA and standard radiotherapy were increased cohort by cohort until the MTD was reached. The radiation dose to the initial large volume was maintained at 40–40.5 Gy and the boost sequentially increased. Severe oesophagitis ($\geqslant$grade 3) was observed in 40% at 50 Gy (1.25 Gy twice daily), 29% at 45 Gy (1.5 Gy twice daily), 67% at 50 Gy (1.5 Gy twice daily) and 86% at 55 Gy, respectively. A similar dose escalation was performed for conventionally fractionated radiotherapy through 56, 60, 66 and 70 Gy. Based on the marked increase in toxicity at higher doses, the MTD was judged to be 45 Gy in 30 fractions for hyperfractionated radiotherapy compared with 70 Gy in 35 fractions over 7 weeks for conventionally fractionated radiotherapy.

In a study of dose escalation using hyperfractionated radiotherapy in NSCLC, the Radiation Therapy Oncology Group (RTOG) [32,33] demonstrated an optimal dose of 69.6 Gy. No additional advantage in survival was achieved by further dose escalation beyond 69.6 Gy. An overview of RTOG trials documented that concurrent chemotherapy with 69.6 Gy and hyperfractionated radiotherapy is associated with a 34% incidence of late oesophageal toxicity [34]. This radiation dose must therefore be approaching the MTD for a SRCT schedule in NSCLC which includes the oesophagus in the high dose volume.

The Intergroup have demonstrated the absence of a dose response for radiation in SCRT in oesophageal cancer. The Intergroup trial (RTOG 85-01) compared chemoradiation to radiation alone [3]. The trial randomised 121 patients to either 50 Gy chemoradiation in combination with 5-FU and cisplatin versus 64 Gy in 32 fractions using radiotherapy alone. This trial is unusual in that it compares an optimal (high) radiotherapy dose of 64 Gy with a lower dose of 50 Gy in the SCRT arm.

Following this successful trial, the Intergroup adopted a higher radiation dose as their chemoradiation schedule in a phase II trial (Int O122) escalating the total dose of radiation to 65 Gy and expanding the chemotherapy to five cycles. The Intergroup proceeded to a further trial (Int 0123) which randomised patients preoperatively to either 50.4 Gy in 28 fractions or 64.8 Gy in 36 fractions in combination with 5-FU and cisplatin as delivered in the RTOG 85-01 trial. Preliminary results presented at ASCO in 2000 [11] appeared to have a higher mortality in the arm receiving 64.8 Gy. This trial did not confirm any difference in 2-year survival for the higher dose of 64.8 Gy. Median survival was 12.9 months for the high-dose arm and 17.5 months for the standard 50.4 Gy.

In the RTOG 9207 study in oesophageal cancer [35], raising the brachytherapy dose did not reduce local failure—although there was a noticeable increase in normal tissue complications at the higher doses.

The failure to demonstrate an advantage for the higher dose may reflect excess treatment-related toxicity and mortality. Normal tissue effects may therefore be

dose-limiting and outweigh any potential tumoricidal advantages from the higher radiation doses.

It is therefore difficult to see any advantage in survival from dose-escalating radiation from any of the above trials.

It may well be that, in future, rather than attempting to escalate the total dose of radiotherapy, clinicians will embrace the strategy of optimising the dose of chemotherapy first and then integrate the MTD of radiotherapy. This approach has recently been undertaken in pancreatic cancer with a combination of gemcitabine and radiotherapy [36]. The authors set the dose of gemcitabine at a full dose (1000 mg/m^2 weekly for 3 weeks). The radiotherapy dose was then escalated from a total starting dose of 24 Gy in 15 fractions of 1.6 Gy per fraction. The radiotherapy escalation increased the dose per fraction in 0.2 Gy increments, but maintained the number of fractions at 15 and kept the overall treatment time at 3 weeks. The total dose reached was 42 Gy without any increase in efficacy. This novel method of optimising the dose of chemotherapy and then escalating the dose of radiotherapy warrants further study in other disease sites.

5.2. What is the optimal scheduling of radiotherapy?

Is the early integration of radiotherapy more effective, or can neoadjuvant chemotherapy shrink a locally advanced tumour and improve oxygenation? Several phase III trials have set out to answer the question of the optimal timing and sequencing of chemotherapy in SCRT in SCLC. The Cancer and Leukaemia Group B (CALGB) randomised 390 patients between early and late thoracic radiation [37]. The study demonstrates an improvement in local control from early radiotherapy but a poorer survival at 5 years (6.6% versus 12.8%)—suggesting that significant reductions in the chemotherapy doses were associated with a loss of systemic control.

It is well recognised that dose intensity of chemotherapy in the first cycle may be crucial [38]. In contrast, a further study [39], randomised 103 patients between initial SCRT using carboplatin and etoposide concurrently with 54 Gy in 36 fractions (1.5 Gy twice daily) against the same schedule during weeks 6–9. Early thoracic irradiation in SCRT appears in this study to confer a reduction in local recurrence from 65 to 42%. In addition, the survival at 5 years improved from 15 to 30%.

A Japanese study of initial SCRT using 45 Gy in 30 fractions over 3 weeks with cisplatin and etoposide showed a significant advantage (median survival 31 versus 21 months) for early over late SCRT during the fourth cycle of chemotherapy [40].

A Canadian study also randomised between early and late SCRT [41] and also showed an improvement in 5-year survival from 11 to 20% for early SCRT. Murray and Coldman further clarified the importance of early irradiation in an overview of 2440 patients from published literature in SCLC [42].

In NSCLC, a large randomised trial from Japan also appears to support the early timing of radiotherapy [43]. In this study, 5-year survival improved from 9 to 16% with early SCRT as definitive treatment. A current German study is attempting to answer the question of whether the early use of chemoradiation improves downstaging and survival when compared with induction with chemotherapy alone [44].

In many of the studies described, local failure remains high. The best results in terms of local control seem to have been achieved by the early concurrent administration of both chemotherapy and radiotherapy. This approach has been confirmed as effective in other disease sites notably naso-pharyngeal cancer [45].

In summary, the trials with the best results in terms of local control appear to have employed a schedule of *early* concurrent chemoradiation.

5.3. Fraction size

Higher total doses of radiation with conventional fractionation may be difficult to achieve because of excess morbidity. Hyperfractionated chemoradiation can offer a therapeutic advantage by limiting the late radiation toxicity to normal tissues. Small gains in locoregional control have been achieved from the use of hyperfractionated or accelerated radiotherapy, but clinically relevant benefits in overall survival have been more difficult to attain.

Early radiobiological experiments suggested that a difference in radiosensitivity exists between early-reacting and late-reacting tissues which can be exploited by reducing the dose per fraction. Late-reacting tissues are less able to repair sublethal damage when large doses per fraction are delivered [46]. The corollary appears to be true and has been examined in greater depth by strategies which include both hyperfractionation and a concomitant boost. In hyperfractionated schedules, the dose per fraction has usually been reduced below 2.0 Gy (usually 1.1–1.5 Gy) and delivered in multiple fractions per day with a 6- or 8-h interfraction interval. For this reason, it is projected that late reacting normal tissues such as the lung, connective tissues, coronary arteries and nerves should benefit in terms of a better therapeutic ratio from hyperfractionated radiotherapy.

The optimal fraction size in the context of SCRT remains a controversial issue. Most clinical oncologists are wary of utilising more than 1.8–2.0 Gy per fraction and larger fraction size has not been systematically investigated. We are not aware of any randomised studies which directly compare fraction sizes in excess of 2.0 Gy being compared with standard fractions (1.8–2.0 Gy per day).

A phase III study from the EORTC in operable rectal cancer [9] randomised between 34.5 Gy in 15 fractions of 2.3 Gy over 18 days with concurrent bolus 375 mg/m^2 of 5-FU in the first 4 days versus the same dose of radiation alone. Either because of the fractionation or the very large field sizes employed, this study was associated with worse survival in the SCRT arm (46% for SCRT versus 59% 5-year survival for radiotherapy alone). An increase in intercurrent deaths appears to account for the difference.

Some more modern randomised trials have employed larger fractions [20]. This study in oesophageal cancer delivered wide field radiotherapy with 2.66 Gy per fraction to a total dose of 40 Gy in a SCRT schedule, and describes acceptable toxicity. However, a recent subsequent study from Cardiff following an identical protocol and using the same fraction size was associated with 30% mortality after surgery [47].

The United Kingdom Medical Research Council (MRC) sponsored a pilot study of preoperative SCRT (the OEO3 study) The study employed synchronous 5-FU, mitomycin-C and cisplatin with 50 Gy in 20 fractions over 28 days, i.e. 2.5 Gy per fraction. This schedule was not taken forward because of unexpected acute toxicity and was not considered appropriate for the basis of a randomised multicentre trial (data not shown).

In contrast, a recent retrospective study from Canada [48] described the use of 5-FU and mitomycin-C combined with a radiation dose of 50 Gy in 20 fractions in 200 patients, i.e. a fraction size of 2.5 Gy. The treatment is described as well tolerated, although 5 patients died of pneumonia within a period of 60 days of starting SCRT and a further patient died of pneumonitis. Furthermore, 2 patients developed an oesophageal fistula and two oesophageal strictures. In the context of only 13% survival at 5 years, late effects may be seriously underestimated.

A phase I/II study of SCRT employed 2.75 Gy per fraction using a concomitant boost technique in combination with low dose cisplatin to a total dose of 60.5–66 Gy in oesophageal cancer [49]. The study concludes "that it is tolerable to treat selected patients having inoperable locoregional NSCLC with 66 Gy in 24 fractions of 2.75 Gy combined with daily administration of 6 mg/m^2." This study reported overall late toxicity in 12/40 patients. Late oesophageal toxicity occurred in 10 of 25 (40%) of patients—although severe grades were only noted in 5%. Radiation pneumonitis did not appear to be a dose-limiting toxicity despite the large fraction size, and severe late morbidity was reported in only 2/21 (10%), which corresponds to other reports in the literature from similar studies. However, it should be noted that only 25–33% of the total length of the oesophagus received high-dose radiation in this study, which may help to explain the apparent tolerability of this regimen. Other studies in oesophageal cancer have more clearly demonstrated that high dose per fraction radiotherapy (3.7 Gy per fraction) in the context of chemoradiation is associated with excess toxicity both acute and late [50,51].

Hyperfractionation with or without acceleration and dose escalation have been shown in head and neck cancer to improve local control without an obvious increase in the incidence of late normal tissue damage [52]. A more recent randomised trial from Vienna using continuous fractionation with 70 Gy in 7 weeks versus continuous hyperfractionated accelerated radiotherapy to a dose of 55.3 Gy in 33 fractions over 17 days with and without mitomycin C [53] demonstrated an improved (48%) locoregional control for the mitomycin C arm compared to radiation alone (32%). Crude survival after a median survival of 48 months was also significantly better for the hyperfractionated arm with the addition of mitomycin (41%) versus the hyperfractionated arm alone (31%) and conventionally fractionated radiotherapy (24%) but at the expense of exaggerated acute toxicity in terms of confluent mucositis.

In contrast, a recent report from the RTOG fails to confirm any benefit of the addition of synchronous chemotherapy in NSCLC to a regimen of hyperfractionated radiotherapy [54]. A recent German study in advanced head and neck cancer also suggests that the gains in efficacy achieved from SCRT may not be so marked when hyperfractionated radiotherapy is delivered [7]. At 2 years, the loco-regional control rates were 51% for SCRT and 45% for RT alone. Two-year survival with local control were 38 and 32%, respectively, but overall survival was not significantly different.

Studies of SCRT with accelerated radiotherapy [55] and hyperfractionated radiotherapy (total dose of 70.2 Gy in twice-daily fractions of 1.2 Gy) have confirmed an advantage in terms of local control and survival over hyperfractionated radiotherapy alone (higher total dose of 75 Gy in twice daily fractions of 1.25 Gy) [56]. Others more recently have promoted the approach of using an accelerated concomitant boost of radiotherapy with concurrent cisplatin [45].

In a novel design, a phase III Intergroup study of SCRT in SCLC [57] compared two radiation schedules at the same total dose, i.e. 45 Gy in 25 daily fractions, concurrently with cisplatin and etoposide chemotherapy against 45 Gy in 30 fractions (1.5 Gy twice daily) over 3 weeks. Complete response and overall response rates were defined as 48 and 87% for daily versus 56 and 87% for twice-daily radiotherapy, respectively. Local failure reduced from 75 to 42% in the group who received twice-daily radiotherapy. Five-year survival rates also improved from 16% for daily and 26% for the twice-daily schedule. The dose must be considered close to the MTD as 13% experienced severe oesophagitis and 17% grade 4 leucopenia. This represents one of the very few

studies which appears to confirm an advantage in terms of local control and survival when the dose intensity of radiotherapy is increased.

A further phase III study maintained the total radiotherapy dose and overall duration of treatment at similar levels [58]. This study compared 50.4 Gy in 28 daily fractions versus 48 Gy in 32 fractions over 5.6 weeks. The latter schedule used a split-course schedule initially delivering 24 Gy in 16 fractions over 1.6 weeks followed after a 2.5-week gap by a further second course of 24 Gy in 16 fractions over 1.6 weeks. Survival was similar in both groups suggesting that both total radiotherapy dose and dose intensity and overall time are all important factors.

Almost certainly, hyperfractionated radiotherapy regimens will continue to be explored, particularly in head and neck cancer, and seem likely to offer an enhanced therapeutic ratio. Recent randomised controlled trials appear to suggest an improvement in locoregional control at the expense of enhanced acute toxicity, but equivalent late damage. There are many different methods currently advocated. Until an optimal radiotherapy regimen/schedule is clarified, it would be inappropriate to consider any schedule in SCRT as a standard.

5.4. Split-course radiotherapy

The combined modality arm from many SCRT studies in head and neck cancer usually has longer unplanned treatment interruptions than the radiotherapy alone arm, although the overall treatment time is similar. Because combination chemotherapy increase both the incidence and severity of SCRT toxicity, several strategies have been developed in an attempt to minimise the acute side-effects. In general, more protracted radiotherapy schedules were explored with built-in treatment gaps [59] and the SCRT was delivered in short intensive cycles [60].

A planned interruption to the radiotherapy schedule—a gap has been used in anal cancer to moderate acute toxicity from SCRT [61,62]. Papillon himself favoured a gap of 8 weeks to allow the slow resolution often described in anal cancer [63]. This approach was integrated into SCRT schedules with 5-FU and mitomycin-C. Early studies using a split-course of SCRT with 5-FU and mitomycin-C in anal cancer do not show any detriment from this approach.

However, split-course regimens of radiotherapy alone are usually considered suboptimal because prolongation of the overall treatment time leads to a reduction in local control [64,65]. These have been documented in head and neck cancer, cervix, bladder cancer and NSCLC, both retrospectively and in prospective randomised trials. The interpretation of retrospective studies may be biased by the association of large fields which may enhance acute toxicity and require a treatment break with more advanced tumours.

The question of overall treatment time and gaps is clarified by the RTOG 92-08 study of SCRT in anal cancer [5]. This pilot phase II study dose escalated to a total dose of 59.4 Gy at 1.8 Gy per fraction with synchronous 5-FU and mitomycin-C, and mandated a 2-week gap at 36 Gy. This followed a previous RTOG phase III trial [28] which involved an identical chemotherapy regimen, but a lower radiation dose of 40–50.4 Gy (median dose 48 Gy) and in which only 11% of patients experienced a 2-week gap. The new schedule represented an increase in total dose from 48 to 59.4 Gy (30% increase), but delivered with a treatment time extended from 5 to 8.5 weeks. Despite the higher total dose, the RTOG92-08 study was associated with a poorer local control.

In the NSCLC study of Schaake-Koning the demonstrated benefit of cisplatin chemotherapy on local control may have compensated for the effect of the planned split-course radiotherapy (which mandated a 3-week gap). Patients were randomly assigned to one of three treatment arms—radiotherapy alone in a split-course regimen which delivered 30 Gy in 10 fractions over 2 weeks followed by a 3-week rest period and then further radiotherapy to a further 25 Gy in 10 fractions of 2.5 Gy over 2 weeks versus the same regimen with either a daily or a weekly schedule of cisplatin [66]. The addition of cisplatin may just serve to overcome the repopulation inherent in a schedule that allows a 3-week rest period.

Subsequent phase II studies from the EORTC (08912) have demonstrated that an identical dose of 55 Gy could be given safely in 4 weeks using a concurrent boost technique [67].

In carcinoma of the oesophagus, poorly designed randomised trials with large fractions (20 Gy) in five fractions repeated after a gap of 14 days [68] have failed to show a benefit. A randomised French study directly compared standard versus split-course radiotherapy (20 Gy in five fractions in two courses during weeks 1 and 5) with concurrent 5-FU and cisplatin-based chemotherapy in 202 patients [69]. Split-course radiotherapy produced higher local failure (73% versus 43% at 2 years) and a worse overall survival (37% for standard radiotherapy versus only 23% for the split-course schedule). This is perhaps unsurprising.

The Geh meta-analysis provides further evidence of a negative influence on the chances of achieving a pathological complete response when the overall duration of radiotherapy during SCRT is increased [23].

In summary, we should not design schedules of SCRT with planned interruptions in the radiation schedule. It is also important to report all enforced interruptions both as frequency and length of time.

6. Conclusion

Clinical successes from SCRT have stimulated interest in further exploring this concept but, to date, very few definitive conclusions can be drawn from the available literature. On present evidence, SCRT should be considered standard treatment in nasopharyngeal cancer, oesophageal cancer, cervical cancer and anal cancer. The role of SCRT in other sites remains a question for further clinical trials.

Based on the evidence from the randomised clinical trials described above, the following recommendations are offered.

1. Fraction size of 1.8–20 Gy is recommended in standard fractionation schedules using total doses of 45–50 Gy in the preoperative setting. Evidence in the literature for delivering higher total doses is insufficient to recommend this approach.
2. Evidence for increasing the fraction size appear sparse and are more likely to be associated with excess acute and possibly late toxicity.
3. Hyperfractionated schedules may have a role to play although the literature suggests the MDT of hyperfractionated regimens in SCRT are lower than with standard fractionation.
4. Split-course schedules are not recommended.
5. The current evidence favours early integration of radiation into SCRT schedules.

Why is there no evidence from randomised trials to suggest that dose escalation of radiotherapy in the context of SCRT improves survival? The majority of studies of SCRT which have shown a significant advantage to SCRT have used wide field radiotherapy (nasopharyngeal cancer, cervical cancer, anal cancer and oesophagus). Most studies have often used intermediate radiotherapy doses in the region of 50 Gy. Dose escalation has only been achieved by limiting the high dose volume to smaller and smaller volumes. It is accepted that large volumes cannot tolerate very high doses. If the benefit in terms of survival from SCRT reflects better control of microscopic disease from wide-field radiotherapy, dose escalation to the primary tumour may not confer any additional advantage. This hypothesis could explain the lack of a dose–response relationship in SCRT.

It is also our hypothesis that the disease sites where SCRT appears most successful are recognised to be sensitive to chemotherapy. Areas where chemotherapy results are poor, such as pancreas, have not reported any similar major benefit. SCRT may therefore offer a greater therapeutic advantage in disease sites where combination chemotherapy can eradicate occult metastases or offer sustained major responses. The present authors advocate optimising chemotherapy in SCRT schedules. Some randomised trials which have failed to confirm a survival advantage for SCRT [70] can be criticised for using a very low dose intensity of chemotherapy. Trovo and colleagues [70] used an accelerated regimen with 3 Gy daily for 15 days to a total dose of 45 Gy concurrently with 6 mg/m^2 of daily cisplatin. This schedule only provides a cumulative overall treatment dose over the 3 weeks of 90 mg/m^2 which may be insufficient.

In support of this view, the mathematical model of Geh and colleagues [23] in oesophageal cancer described above, suggests that the relative contribution of chemotherapy to the chance of a histopathogical complete response may be much higher than that of radiotherapy.

Since the risk of late damage inevitably escalates with increasing radiation dose, it seems more logical in SCRT to optimise the chemotherapy rather than to focus on dose escalating the radiation. For this reason, the Colorectal Clinical Oncology Group (CCOG) in the UK is embarking on a long-term programme examining the most effective chemotherapy schedules which will optimally integrate with standard fractionation radiotherapy with standardised field sizes. Chemotherapy effects should not be permanent. Given an optimal chemotherapy regimen, which is effective in the context of metastatic disease, the strategy then aims to integrate a low dose of radiotherapy (30 Gy in 25 fractions of 1.2 Gy). In a standard phase I mechanism, the aim would be to dose escalate the radiotherapy fraction size (1.4, 1.6, 1.8 and 2.0 Gy) until the MTD is reached. Hopefully, this strategy offers an optimal trade off between toxicity and efficacy by reducing late toxicity for similar or even possibly greater efficacy.

The enhanced acute toxicity and persistent high risk of local failure in many disease settings with current SCRT schedules demand that more effective and less toxic treatment strategies must be identified in the future and tested in randomised trials. Phase I studies are also essential with the emphasis on meticulous reporting of acute toxicity end-points and documenting the field sizes or proportions of critical organs within the high dose area if we are to derive the optimal therapeutic ratio. It will prove a major challenge to design and evaluate such studies.

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