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Review

Non-small cell lung cancer and CHART (Continuous Hyperfractionated Accelerated Radiotherapy) – where do we stand?

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SUMMARY

This paper reviews the use of hyperfractionated and/or accelerated radiation therapy in the curative treatment of non-small cell lung cancer, and explains the scientific rationale behind the development of these regimes. The indications, practicalities and economics of introducing them routinely are addressed. Novel radiotherapy techniques are further discussed in the context of current developments and on-going clinical trials.

INTRODUCTION

The estimated average incidence of non-small cell lung cancer in Northern Ireland is over 750 new cases per year.[1] Up to 20% of patients may be suitable for a surgical approach – of those who do have resection (estimated at less than 10% in Northern Ireland), fewer than half will be long term survivors. Tumour-related reasons for inoperability include local invasion and spread to mediastinal lymph nodes. Over the last 3 years, an annual average of 450 patients with lung cancer were referred to the Northern Ireland Centre for Clinical Oncology (NICCO). In 1994, 331 new lung cancer patients received radiotherapy treatment. Extrapolating from fractionation statistics, about 280 patients were treated for NSCLC, of which 38 received radical radiotherapy. This is in keeping with a recognised figure (~10%) for the proportion of patients referred for radiotherapy who have stage I/II disease and are suitable for small volume radical radiotherapy. Standard radical radiotherapy involves treating a planned volume once daily, five days per week, for up to 6 weeks. In the 30-40% who have unresectable locally advanced disease confined to the thorax, survival is of the order of 40% at one year and 15-20% at two years. Failure rates and patterns have been well documented, and indicate an intra-thoracic failure rate of up to 48%, depending on stage, histology and radiation dose delivered.[2] Up to three-quarters of these failed with distant metastases, therefore the role of systemic chemotherapy continues to be widely studied. Nonetheless, many die of uncontrolled intra-thoracic disease and methods of improving the radiotherapy technique which might improve survival, need to be pursued. In recent years non-standard fractionation schedules have been studied in clinical trials for different disease sites. In 1997 a large multicentre prospective randomised controlled trial was reported in the Lancet describing a highly significant survival advantage for locally advanced NSCLC using CHART.[3] This regime involves using smaller fraction sizes, three times per day for a continuous 12 day period. There are obvious practical and economic implications if this were to be made routinely available. The potential health gain in this common disease cannot be ignored.

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BACKGROUND

The concept and advantage of fractionating radiotherapy was recognised clinically within the first 25 years after the discovery of x-rays by Roentgen in 1895. It was Regaud in France, who reported in 1927 that a ram could be sterilised and the scrotal skin spared if x-rays were delivered in several smaller daily doses rather than one large dose.[4] This astute observation, although fundamentally not applicable to treating a tumour located deep to normal tissue, opened the door to many fractionation experiments in subsequent years.[5]

It was in the 1940s that experimental radiobiology studying mammalian cells in culture, began its evolution, and very soon the clinical and laboratory efforts became clearly complementary. By the 1970s, the concepts of normal tissue tolerance and tumour cell kinetics were becoming much better understood. Attempts were made to develop mathematical models to help explain the phenomena of different tissues responding in different ways. If this could be done, then extrapolation might be able to suggest how to improve further the therapeutic index – in other words, how to gain better tumour control without causing further significant damage to the normal tissues unavoidably encompassed within the treatment field.[6,7] This is precisely the way in which a better understanding has been achieved, thus leading to the phase III clinical trials which are described later.[8,9] Understanding the effects of radiation at a molecular level may provide further information on which to develop and optimise clinical radiotherapy.[10]

Although not perfect, it is the linear-quadratic model on which much has been based to date. This model is derived from experimental cell survival curves worked and their shape or 'curviness', as shown in Figure 1. At a lower dose (D1), more damage occurs in acute reacting tissues such as skin or mucosa. As the dose (per fraction) increases (D2), there is a higher probability of damage to late reacting tissues such as spinal cord, lung or kidney. Reproductive capacity of a cell determines its radiobiological survival, partially determined by its ability to repair sub-lethal or potentially lethal damage which has been caused by radiation. In vitro half-time repair of normal tissues has been observed to be between 0.5-2.0 hours. When more than one fraction per day is given, the optimum rest period in order to

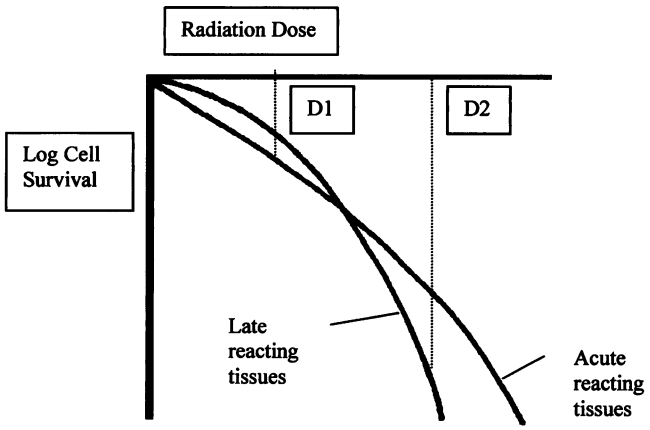

Fig 1. Cell survival curves for acute and late responding responding tissues.

allow maximum normal tissue repair between fractions, has been calculated to be 3-8 hours. The theory of what shares a tissue's cell survival curve involves the 'hit' theory of radiation on DNA, and whether a single-stranded break (SSB) or a double-stranded break (DSB) has occurred. As the number of SSBs increases, the likelihood of that cell not surviving increases linearly, (represented by α). As the number of DSBs increases, the likelihood of that cell failing to replicate increases exponentially, (represented by β). From these parameters, a formula can be derived to closely represent the experimental observations. An α/β ratio can thus also be derived, and for acute reacting tissues such as skin and mucosa it is well represented by a high value of 10, whereas for late reacting tissues such as lung or central nervous system, it is better represented by a low value of around 3. Tumour cells resemble acute responding tissues, and have a high α/β ratio. It has been observed that it is the *dose per fraction* which is the key determinant of late morbidity, whereas the overall treatment time is important for acute morbidity and effect on tumour. It would seem that certain tissues (eg. spinal cord), have a better capability of repair at lower doses per fraction.

The other aspect of radiobiology which is important to the understanding of the rationale behind the design of current fractionation trials, is tumour cell kinetics.[11] Although it can take often months for a tumour to clinically double in size, flow cytometry studies using bromodeoxyuridine to label cells have shown that the real or potential doubling time (Tpot) is of the order of 7 days, (2.3-5 days for lung tumours). The reason for this discrepancy is that

90% of the growing tumour cells are shed, apoptose, differentiate, or simply do not survive, and this is known as the 'cell loss factor'. It is particularly high in squamous cell carcinomas. When a dose of radiation is given, many cells will be killed, but as a result there will be re-vascularisation and re- oxygenation of the remaining cells, allowing improved nutrition and thus survival of a proportion of cells which would otherwise not have survived. The result of this, and other factors, is rapid tumour cell repopulation. Taking these main radiobiological considerations into account, fractionation schemes have been developed – low doses per fraction reduce late normal tissue damage, and shorter overall treatment time achieves maximum tumour kill allowing less tumour cell repopulation during treatment.[12, 13]

In conventional fractionation, doses of 2 Gray are delivered once each day, five days per week. Overall treatment times are normally around six weeks. In *hyperfractionation*, smaller doses per fraction are delivered two or three times per day, leaving the overall treatment time unchanged. This approach theoretically allows the total tumour dose to be escalated without increasing late morbidity, thereby improving the therapeutic index. In a recent review of hyperfractionated radiotherapy in human tumours, it was consistently demonstrated to be more effective in terms of responses than was conventional radiotherapy. However the methodology used to collate the information in this review has been critisized.[14] In *accelerated radiotherapy*, treatment is delivered in a shorter overall time, leaving the fraction size unchanged. The theory behind this is to reduce the amount of tumour cell repopulation during the treatment course. Several different strategies may be employed:

1. A straightforward short intensive course – total dose must be reduced because of otherwise significantly increased acute tissue toxicity.
2. Split-course technique – a rest period is introduced between the second and fourth week of treatment which allows acute normal tissue regeneration to occur so that total dose does not need to be reduced.
3. Concomitant boost technique – the second phase or small volume is given concurrently rather than sequentially.
4. Escalating dose – the total weekly dose is increased each week. It is thought that the regeneration of normal mucosa is stimulated early in the treatment course and might therefore be able to tolerate higher doses as the course is delivered.

By combining hyperfractionation and accelerated radiotherapy, continuous hyperfractionated accelerated radiotherapy or CHART was developed, represented diagrammatically in Figure 2, in order to maximise the potential gain.[15] This technique uses smaller multiple fractions per day and therefore a lower overall total dose. The acute tissue injury occurs only after the course is completed, and can therefore be allowed to heal and regenerate without the problem of having to complete treatment.

The Radiation Therapy Oncology Group (RTOG) published a preliminary report of a prospective randomised study of various irradiation doses and fractionation schedules in the treatment of inoperable carcinoma of the lung, in 1980.[16] Radiological complete response (CR) rate was 10-25%, and 2-year survival only 12%. From this, the exploration of novel radiotherapy schedules has mushroomed, in a determined effort to find the optimum scheduling. Laboratory studies have played a huge part in painstakingly and scientifically providing the basis of clinical studies.

METHODS

The literature was reviewed using Medline, and authoritative texts reviewed. A search was conducted for all papers and specifically all clinical trials in hyperfractionated or accelerated radiotherapy. Fewer than 15 review articles

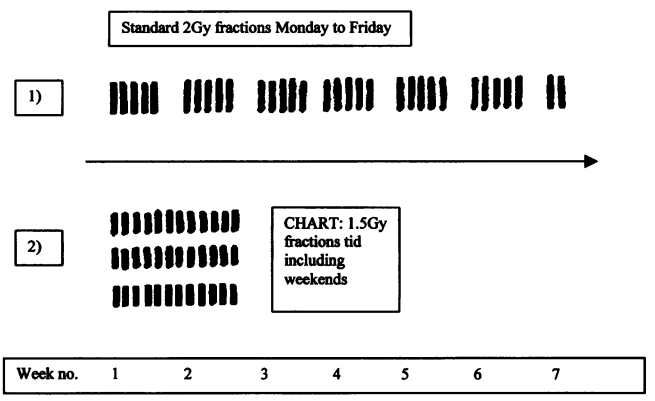

Fig 2. Diagramatic representation of standard and CHART radiotherapy fractionation schedules.

relating primarily to fractionation of radical radiotherapy for NSCLC since 1985 were identified. In these, the role of combined chemo-radiation is discussed prominently.

The practical questions of staffing, and changes required in any radiotherapy department considering introducing these techniques, is not adequately addressed, although any additional cost of multiple daily fractions, has been analysed in detail recently.[17] Information was also obtained from the Radiotherapy Department at NICCO, from the Northern Ireland Cancer Registry at Royal Victoria Hospital, and from the Belfast City Hospital.

CLINICAL TRIALS IN NON-SMALL CELL LUNG CANCER

It has been shown that improving local control is a prerequisite for improving overall survival.[18] An RTOG pilot study in 1985 studied 120 patients who were treated with 1.2Gy fractions twice per day, to total doses ranging form 50.4Gy up to 74.4Gy.[19] There was a 13% complete response rate (CR) and a 33% partial response rate (PR), although the severe late complication rate was 10% with doses greater than 60Gy. Median survival overall was 7.2 months, compatible with other studies giving standard radiation. In 1990, an RTOG randomised phase I/II trial of 848 patients, compared total doses ranging from 60Gy up to 79.2Gy over 5-6½ weeks, given again in 1.2Gy fractions twice per day.[20] Although sub-group analysis must be regarded with some caution, the authors noted that in good performance status patients with stage III disease, a significant survival benefit was seen as the dose was escalated to 69.6Gy, but not thereafter (2-year survival of 29% in favourable stage III). There was no increase in acute or late tissue toxicity.

Regarding predominantly accelerated radiotherapy for NSCLC, a study in 1986 reported 17 patients who were treated with 1.8-2Gy fractions, twice per day to a total dose of 66Gy in less than four weeks.[21] There was a 40% CR, but all experienced oesophagitis, and 24% had severe complications. In another small study, only 12 patients were reported, and four of these had small cell lung carcinoma.[22] The main interest here was in describing a novel three-times per day fractionation schedule which achieved the aim of accelerating treatment but not altering normal staffing levels. Out of only eight patients with NSCLC given 1.1 Gy twice daily, there were six patients (75%) who achieved a complete response (CR) at the primary site of disease, although not all of these patients had a CR at the nodal site as well.

On the basis of the results of the RTOG randomised phase I/II study, a phase III randomised trial was conducted, and this included 452 patients with inoperable intra-thoracic disease (stage II-IIIB).[23] Standard radiotherapy was compared to hyperfractionated radiotherapy and also to induction chemotherapy followed by standard radiotherapy. In the combined chemo-radiation arm the median survival was 13.8 months, and was statistically better than the standard or the hyperfractionated radiotherapy arms (median survivals of 11.4 and 12.3 months respectively). However, a recent up-date has suggested that this benefit was confined to histologies other than squamous cell carcinoma.[24]

Since the early seventies, the RTOG has conducted a number of prospective trials in an attempt to clarify the role of radiation in NSCLC.[25,26] In 1988 an RTOG pilot study looked at 56 patients who were given 75Gy in 28 fractions over five-and-a-half weeks.[27] Daily dose to the mediastinum was 1.8Gy and 2.68Gy to gross tumour. Out of 44 patients who received the prescribed dose, there was a 72.7% response rate with 17 CRs and 15 PRs. Follow-up ranged from 1-3 years; at the time of reporting, there were nine patients alive and disease-free and five who died of intercurrent illness. Twenty-four had died of known tumour.

The concomitant boost technique was tested in an RTOG phase I/II trial in 1993.[28] Three hundred and fifty-five patients were entered, and the total dose was escalated from 63Gy in 5 weeks (45Gy plus 18Gy boost) up to 70.2Gy in 5.5 weeks (50.4Gy plus 19.8Gy boost). The final 114 patients received 70.2Gy in 5 weeks. Severe acute toxicity occurred in 2-3% of patients, and late morbidity was up to 9% overall. Two year survival rates ranged from 16% in the earlier patients to 21% in the later patients. At a similar stage, a phase I/II trial involving 37 patients was reported.[29] They were treated with 2Gy fractions twice per day to a total dose of 50Gy in 4 weeks. There was no increase in acute or late morbidity and 3-year survival was 10%. An RTOG phase I/II study of 59 patients with T3/T4 NSCLC, treated with the concomitant boost technique was reported in 1995.[30] Treatment was given on 5 days per week,

2.68Gy per fraction to the primary tumour over 5.5 weeks. Total dose was 75Gy in 28 fractions. Median survival was 10 months and only 3 patients had severe late complications. It was concluded that this was a feasible technique with acceptable late toxicity and comparable survival rates to the best reported in the literature using either hyperfractionated radiotherapy or combined chemo-radiation.

A prospective trial of split course versus conventional radiotherapy was reported in 1995.[31] Two hundred and seventy-three consecutive NSCLC patients were randomised, and all were staged, treated and followed up by a single physician in an attempt to maintain uniformity. No difference in survival was found between the two arms, median survivals being 11.6 and 10.9 months respectively. The split course arm was associated with less morbidity.

A pilot study of accelerated hyperfractionated thoracic radiation therapy (AHTRT) for unresectable stage III NSCLC was reported in 1993.[32] The main endpoint was toxicity. Twenty-one patients were treated with 60Gy in 40 fractions giving 1.5Gy twice daily with a 2-week break midway through treatment. The median survival was 10.8 months. The 1 and 2-year survival rates were 48% and 29% respectively. Three year survival was 14%. Because of these encouraging results, a further study has since been initiated comparing standard radiotherapy against AHTRT +/- chemotherapy.

In 1990, a phase I/II trial of continuous hyperfractionated accelerated radiotherapy, or CHART, was reported.[33] Sixty-two patients with locally advanced NSCLC received 50.4Gy escalated up to 54Gy, given in 1.5Gy fractions three times per day on 12 consecutive days. Oesophagitis was the only notable complication but was not severe, and 42% went into radiological CR. The 2-year survival was 34%. As a result of these findings, a phase III randomised controlled clinical trial was conducted.[3] Five hundred and sixty-three patients were entered, and randomly allocated in a 3:2 ratio for CHART or conventional radiotherapy (60Gy in 30 fractions over 6 weeks). Patients with stages IA-IIIB lung cancer and good performance status were included. Two-year survival was improved from 20% to 29% (p=0.004, see figure 1) and subgroup analysis indicated that the largest benefit for the accelerated regime occurred in the 82% of patients who had squamous cell carcinoma. In this subgroup, 2-year survival increased from 19% to 33%. Overall, there were no significant differences in acute or late morbidity. As a follow-on from this, CHARTWEL (CHART weekend-less) is being piloted with a view to maintaining the radiobiological advantage whilst producing less interference with normal working patterns.

ECONOMIC AND STAFFING IMPLICATIONS

The cost of treating with a course of radiotherapy has not generally been a significant part of overall analyses before, but then recommending routine out-of hours radiotherapy treatments has not until now, been a prominent issue.[34] It has been argued however, that sub-optimal radiotherapy is more costly in the long run.[35] CHART was used in 10 UK centres during the 2 major trials for both bronchus and for head and neck cancer. The cost of CHART versus conventional radiotherapy was compared,[17] and CHART was not suprisingly found to be more expensive. However, for NSCLC, the difference was calculated to be £698 per patient (less if a hostel ward is available, which is the case at NICCO). If CHARTWEL proves to be as effective as CHART, then not only would the cost be reduced further, but the important issue of staff working times would not be as significant. It is also acknowledged that these costs relate only to treatment, and not to the longer term gain of disease-free or overall survival which in turn reduces the need for palliative and supportive care facilities.

Out of 280 NSCLC patients who had radiotherapy in 1994, at NICCO approximately 40 had radical radiotherapy, and 240 palliative radiotherapy. It can only be estimated how many out of the 240 would have had locally advanced disease, and of those, how many might have been suitable for CHART. Given that only 5% of patients referred for CHART were suitable for inclusion in the randomised trial,[36] then perhaps 12-15 patients from this cohort might have been suitable for entry. Allowing for an increase in the number of referrals over the last few years, it is projected that a total of 60-70 patients per year might be offered an accelerated radiotherapy regime. Additionaal total funding could therefore be estimated to be £40,000-£45,000 per year. In contrast, the expenditure on new chemotherapy drugs in the UK is estimated to be up to £18,000 per patient treated.[37]

OTHER ASPECTS OF RADIATION THERAPY DEVELOPMENT

The place of more intensive fractionation schedules has been evaluated in a number of other situations. The most promising is in head and neck cancers, although the smaller incidence and obvious heterogeneity create inherent difficulties in showing statistical differences in overall or disease-free survival. There have been encouraging results indicating trends towards better local control for more advanced disease (T3/T4).[38, 39] There is equivocal evidence at present in oesophageal carcinoma,[40, 41] bladder transitional cell carcinoma, prostate cancer and malignant gliomas.

Another main area of development in radiation oncology, is the use of conformal radiotherapy (CFRT). Rather than using rectangular fields and lead shielding to modify the shape of the beam, multi-leaf collimators (MLCs) have been developed which enable a more finely shaped beam to be delivered.[42] Three dimensional treatment planning is being used and assessed in many centres throughout the United States and Europe.[43, 44] Preliminary results for lung cancer indicate a 2-year cause-specific survival of 90% for stage I/II and 53% for stage IIIA/B.[45] With improvement in technology and lower costs, there is considerable anticipation.[46] In addition, Intensity Modulated Radiation Therapy (IMRT) is a yet further advance in the ability to deliver more precisely shaped dose distributions, and is created by varying the intensity of the beam across the treatment field. The first patient was treated using this technology in Houston, Texas, in March 1994, and by July 1997, more than 500 patients had been treated using IMRT at 14 institutions.

However, no technology nor combination of other treatment parameters can make up for geographically missing microscopic tumour, so it is therefore vital that imaging and other aids to defining tumour volume and therefore target volume continue to be actively explored.[47] The logic behind physically reducing the amount of normal tissue in the treatment volume is self evident, and dose responses have indeed been shown for locally advanced NSCLC.[48] The ability to dose escalate without increasing normal tissue damage using a conformal approach is undoubtedly exciting, however the benefits will need to be demonstrated by prospective randomised controlled trials before it should be recommended for routine use in the UK. The first of these trials by the Medical Research Council (MRC) in prostate cancer, is already underway.

The idea of optimising radiotherapy either by fractionation schedules, beam shaping, or both, is now the focus of many studies. The selection of patients most likely to benefit from these techniques is crucial, and it may be that using specific assays to determine clonogen doubling time, patients could be more accurately selected for CHART (short Tpot) or concomitant boost accelerated radiotherapy (longer Tpot).[49, 50] Other ways to enhance the tumour kill effect of radiation are with the use of radiosensitisers such as misonidazole,[51] or the concurrent breathing of carbogen and nicotinamide,[52] but these techniques remain experimental. Intraluminal brachytherapy (or radiation delivered from a source, rather than external beams) is also of interest, but as yet has no defined place in the radical treatment of NSCLC.

An interesting concept that is currently under investigation, is bio-effective dosimetry.[53] This has potential to produce treatment plans based on biological effect, rather than absorbed dose, to any given point. Although there is a long way to go before this could be introduced to clinical departments, it is one of the many ways in which the planning and delivery of radiation may be yet further advanced.

CHEMOTHERAPY FOR NON-SMALL CELL LUNG CANCER

The place of systemic chemotherapy in NSCLC has been widely investigated, and there is now evidence that a modest survival advantage can be achieved.[54] Many investigators are therefore looking at chemo-radiotherapy combinations, using platinum-based chemotherapy and intensive fractionation,[55] however there are still reasonable concerns about toxicity.[56] Similarly, with increasing evidence of benefit for combined treatment in unresectable oesophageal carcinoma,[57] the possibility of enhancing local control even further with intensified radiotherapy needs to be investigated. Indeed, the ultimate search for a combination of optimised radiotherapy and the most effective systemic chemotherapy in unresectable tumours, provides considerable material for on-going and future clinical trials.

CONCLUSIONS

While results of surgical resection for early tumours are good this disease has a poor prognosis controlling intra-thoracic tumour in this common disease should be a priority in cancer research and management. Of many possible ways, and combinations of ways, to approach this problem, CHART has shown a statistically significant benefit in a large multi-centre randomised controlled trial. However, adopting this technique into routine clinical practice requires more resources and careful patient selection.[58] Two years on after publication, only a few UK Centres find themselves able to offer CHART to selected patients, and the reasons for this are clearly outlined in a recent editorial.[59] The bottom line includes difficulties in changing departmental working hours, and lack of financial support. There is no real doubt that it ought to be made available; however the practicalities of its introduction as an available standard, should not be underestimated.

Novel and developing radiation therapy must be incorporated as an intregal part of modern cancer management. It is essential that participation in national clinical trials is encouraged, that radiotherapy techniques are optimised, and that combined modality approaches are able to be fully supported.

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