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Comments and Critique

Study Design in the Evaluation of Combined Radiotherapy Plus Chemotherapy

INTRODUCTION

COMBINED RADIOTHERAPY and chemotherapy in both animals and man has been well reviewed [1, 2]. Clinical trials have identified several methodological issues that limit interpretation, including study design and the choice of normal tissue endpoints. We have explored two such issues in the context of combined modality treatment.

Randomised trials of combined modality treatment ask two kinds of question, which are not always clearly distinguished. The first relates to what we define as therapeutic gain—i.e. whether the addition of a second modality contributes something extra to local control and/or survival at equal levels of dose-limiting toxicity that cannot be achieved with a single modality on its own. The second concerns the "clinical usefulness" of a combined treatment, taking into account all the toxic side-effects, regardless of whether they are dose-limiting.

Combined modality therapy vs. radiotherapy alone

Therapeutic gain occurs only when the enhancement of tumour response by a drug–radiation combination exceeds the enhancement of critical normal tissue responses. Enhancement in this context is defined as a clinical effect greater than that seen with single modality treatment. In a two-arm trial comparing radiation plus drugs with radiotherapy alone, enhanced local control must be achieved with equal toxicity in both arms. A randomised trial of radiotherapy with and without chemotherapy, with equal doses of radiotherapy in both arms, runs the risk of being uninterpretable if enhanced tumour control in one arm co-exists with enhanced early/late normal tissue toxicity (Table 1). If the comparison had been confined to arms I and II, equivalent levels of local control and toxicity might have been equally well achieved with an increased dose of radiation alone (i.e., arm III).

Even if a randomised comparison of radiotherapy with and without chemotherapy reports better tumour control with equal complications, this may be because the normal tissue endpoints were not sensitive enough to reveal real differences. This is more likely when severe complications are used as the sole basis for comparison. From Table 1, therapeutic gain for arm II might be claimed on the basis of equal severe complications, whereas the frequency of moderate toxicity has risen steeply. Severe complications are clinically relevant and dose-limiting but they are not suitable as the sole endpoints for comparison because the number of events is usually small. A 5% rate of severe complications at 60 Gy may double to 10% at 65 Gy but this important difference requires over 1000 patients to discriminate. A less severe side-effect occurring at a higher frequency on the steeply rising portion of the dose–response curve will be more sensitive to small differences in dose (Fig. 1). A side-effect experienced by 30% of patients at 60 Gy may affect 50% at 65 Gy, requiring only 220 patients to discriminate (one-tailed test, false positive rate = 5%, false negative rate = 10%). At the other extreme, a mild side-effect as an endpoint will be unhelpful because virtually all patients will score regardless of dose.

There is no easy way to resolve the difficulty of interpreting a two-arm trial but a third treatment arm testing a higher dose of radiotherapy alone may be the best approach, despite the implications for increased patient numbers and levels of complications (Table 1). Arm III introduces a slightly higher dose of radiotherapy alone against which the enhanced moderate toxicity in arm II can be compared. Equivalent levels of local control and toxicity would have been achieved with a higher dose of radiation alone.

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Table 1. Therapeutic gain in a hypothetical randomised trial of radiotherapy (RT) plus or minus chemotherapy (CT)

Treatment	Local control (%)	Local toxicity (%)		
		Severe	Moderate	Mild
Arm I				
RT (60 Gy) alone	50	< 10	30	> 90
Arm II				
RT (60 Gy) plus CT	70	< 10	50	> 90
Arm III				
RT (65 Gy) alone	70	< 10	50	> 90

For example, in the treatment of ano-rectal carcinoma, enhanced early and late normal tissue responses may occur when radiotherapy, 5-fluorouracil (5FU), and mitomycin-C (MC) are combined. In a historical case-matched control study [3] of 55 patients treated with 50 Gy in twenty fractions with or without 5FU/MC, the addition of 5FU/MC to radiotherapy increased local control from 15 out of 25 patients (60%) to 28 out of 30 (90%). Serious late complications requiring surgery occurred in 3 patients (12%) treated by radiotherapy alone and 5 (17%) receiving both modalities (not significant). 4 (16%) and 14 (47%) patients, respectively, had acute toxic local events—i.e., clinically significant enhancement of radiation toxicity.

In this situation, a randomised comparison of radiotherapy plus or minus 5FU/MC with the same dose of radiotherapy in both arms would be almost impossible to interpret. A third arm with a 5–10% higher dose of radiotherapy alone would help interpretation. The increased level of toxicity associated with this higher dose is thus justified. The only possible alternative is a two-arm trial with a reduced dose of radiotherapy in the combined modality arm, which risks making the wrong adjustment.

In diseases such as stage III cancers of the head and neck, cervix and bladder, up to half the patients have occult metastases

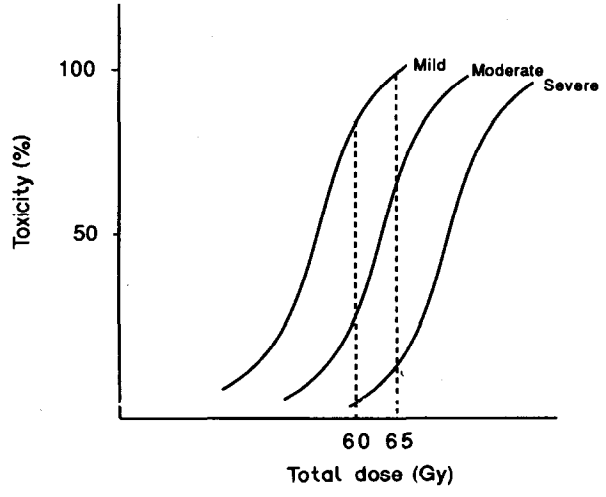

Fig. 1. Radiation dose-response curves for three levels of early and/or late toxicity.

Table 2. Therapeutic gain in a hypothetical combined modality trial: drug effects on occult metastases

Treatment	Local toxicity (%)	Local control (%)	5 year survival (%)
Arm I			
RT (60 Gy)	30	50	25
Arm II			
RT (60 Gy) plus CT	50	70	50
Arm III			
RT (65 Gy) alone	50	70	35

at presentation. Radiotherapy remains the main curative non-surgical modality but it is reasonable to ask if cure is increased by an effect on metastatic disease as well as from enhanced local control. In this common situation a three-arm design retains its advantages (Table 2). There is no suggestion of therapeutic gain in local control, but there appears to be a significant gain in survival after combined modality treatment arising from a drug effect on metastases. However, the third arm is needed to assess the impact of improved local control on survival if the chemotherapy effect on metastases does not materialise.

Systemic toxicities (e.g., neutropenia with septic complications) have been omitted from our hypothetical trials despite contributing significantly to the overall toxicity and affecting clinical usefulness. Only the toxic effects of radiotherapy contribute to the calculation of therapeutic gain as we define it. For example, drug-induced hair loss is an obvious example of a side-effect that is not relevant to therapeutic gain because it is not dose-limiting for the radiotherapy. Drug-induced neutropenia is also irrelevant except in uncommon circumstances where it might limit radiation doses, such as in total nodal radiation. On the other hand, dose-limiting radiation reactions that are enhanced by chemotherapy are critical to calculation of therapeutic gain. The overall systemic toxicity of combined modality treatment often exceeds the systemic toxicity of radiotherapy alone, and these additional toxicities may limit the appeal of combined treatment as a practical option for all patients. To determine therapeutic gain when radiotherapy is the main curative modality, only toxicities arising inside the treatment volume need to be balanced between trial arms because only these are influenced by higher doses of radiotherapy alone (Table 3).

Improving cure by adding radiotherapy to chemotherapy

Our arguments in favour of three-arm trials apply only if radiotherapy alone is the established treatment, and the role of added chemotherapy is under evaluation. Once these roles are reversed the definition of therapeutic gain requires modification. When synchronous or intercalated chemo-radiotherapy is being delivered, modifications to the drug schedules are often necessary in response to enhanced haematological toxicity. As a result the dose-limiting toxicities of combined modality therapy compared with chemotherapy alone may be more or less equalised as treatment proceeds. There will be additional toxicities arising within the radiotherapy fields but these do not affect therapeutic gain as we define it. The implications for trial design are that if acute dose-limiting systemic toxicities can be balanced between arms by modifying individual chemotherapy schedules

Table 3. Requirements for demonstrating therapeutic gain in combined modality treatments

Sites of dose-limiting toxicity	Requirement for balanced dose-limiting toxicities	
	Within RT volume	Outside RT volume
Within RT volume*	Yes	No
Outside RT volume†	No	Yes

*Usually trials of RT plus or minus CT (occasionally CT plus or minus RT).
†Always trials of CT plus or minus RT.

as treatment proceeds, two-armed comparisons are probably adequate.

For example, in the Cancer and Leukaemia Group B randomised trial of chemotherapy with or without thoracic radiotherapy in patients with limited-disease small cell lung cancer [4], two alternative combined modality schedules were compared with radiotherapy (50 Gy over five weeks) starting in week one or nine. We shall compare chemotherapy plus radiotherapy in week one with chemotherapy alone. As expected, toxicities were more frequent and severe in the combined modality arm. With chemotherapy alone the median white cell nadir for the first three courses was 2.7×10^9/l, whereas with radiotherapy plus chemotherapy the nadir dropped to 1.3×10^9/l. The proportion of patients requiring a reduction in drug doses was 15% with chemotherapy alone and 52% with chemotherapy/radiation. Even so, more patients had septic complications (20% *vs.* 8%) and oesophagitis (10% vs. zero) in the combined modality arm. At three years 13% of patients given chemotherapy alone achieved local control compared with 54% of patients given combined modality treatment.

The excess local toxicity (oesophagitis) in the combined modality arm is not relevant to the calculation of the therapeutic gain because only the dose-limiting toxicities of the main curative modality need be balanced between the two arms for us to be satisfied that equivalent survival rates could not have been achieved just by intensifying the chemotherapy (Table 3). Despite the imbalance in systemic toxicity (sepsis) between the treatment arms, it is unlikely that the same levels of local control could have been achieved with higher doses of chemotherapy alone because high thoracic recurrence rates are reported even after high-dose chemotherapy requiring marrow transplantation [5]. Unfortunately, even though local control was better there was only a small trend in overall survival favouring the combined modality treatment, and more than 90% patients died of metastatic disease regardless of treatment.

CONCLUSIONS

When radiotherapy is used as the main curative modality, a three-arm design is the surest way to estimate therapeutic gain reliably. Even if a three-arm trial is impractical, it is useful to specify the toxicities relevant to the measurement of therapeutic gain. When radiotherapy is the main curative modality, the side-effects influencing therapeutic gain are dose-limiting toxicities (early or late) arising inside the target volume, because only these are affected by higher doses of radiotherapy alone. Radiochemotherapy may be associated with significant additional toxicities arising outside the irradiated volume that are not dose-limiting for the radiotherapy. These toxicities are not relevant to estimation of therapeutic gain but may be important in determining the clinical usefulness of the combined schedule.

The argument in favour of a three-arm design rests on the timing of the dose-limiting complications rather than the modality causing them. Most dose-limiting complications from radiotherapy occur months later so treatment cannot be individually titrated to a predetermined level of dose-limiting toxicity. Dose-limiting reactions that arise early, as occurs with a continuous course of multiple fractions per day, may force modifications to the combined modality schedule in individual patients as treatment progresses. This may effectively balance the dose-limiting toxicities in each arm of a trial as the study progresses. In this situation, a two-arm trial design may be sufficient.

When chemotherapy is the main curative modality, the dose-limiting side-effects usually arise outside the irradiated zone. Only these are important in determining whether equivalent levels of survival would have been achieved with higher doses of chemotherapy alone. Radiotherapy to local–regional disease may enhance these dose-limiting complications as well as contributing additional early or late toxicities within the irradiated zone (e.g., oesophagitis). Such side-effects are seldom dose-limiting for chemotherapy, but may be important in deciding the clinical usefulness of a combined schedule.

An improved therapeutic gain from combined modality treatment is necessary but not sufficient to make combination therapy generally desirable. After a trial has demonstrated therapeutic gain from combined treatment in terms of local control and/or survival compared with a single modality, the question is whether the superior results and additional toxicity are clinically useful. The answer may depend on the individual patient and involve the clinicians in a value judgement.

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