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Status of hypofractionated radiotherapy in breast cancer

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It has been assumed that in the case of a majority of tumours hypofractionation radiotherapy is of limited value because it negatively affected the ratio of curability to late adverse effects. However, there now exists data to suggest that hypofractionation may be advisory in breast cancer. The author presents a number of recently published and currently ongoing trials, which may provide evidence for the use of hypofractionated radiotherapy in breast cancer patients. The possible implications for primary breast cancer are that modest increase in fraction size combined with reduction in treatment time may translate into worthwhile gains in tumour control, without enhanced late normal tissue injuries. This may affect future decision-making in the course of radiotherapy for breast cancer if the onging trials are confirmatory.

Znaczenie hipofrakcjonowania w radioterapii raka piersi

Hipofrakcjonowanie miało dotychczas ograniczone zastosowanie w radioterapii ze względu na związane z nim niekorzystnie przesunięcie odsetka istotnych odległych efektów ubocznych w stosunku do wyleczeń. Pojawiły się jednak dane sugerujące, że hipofrakcjonowanie może być korzystne w radioterapii raka piersi. Autor przedstawia wyniki niedawno opublikowanych badań klinicznych dotyczących hipofrakcjonowania w radioterapii raka piersi oraz omawia badania będące obecnie w toku. Badania te mogą dostarczyć danych przemawiających za wprowadzeniem tej metody – niewielkie skrócenie czasu leczenia radioterapią może przełożyć się na istotną poprawę kontroli onkologicznej, a jednocześnie nie nasilać występowania późnych reakcji po radioterapii.

Key words: radiotherapy, hypofractionation, breast cancer
Słowa kluczowe: radioterapia, hipofrakcjonowanie, rak piersi

The traditional assumption is that human tumour responses are relatively insensitive to fraction size compared to dose-limiting late reacting normal tissues. This assumption is consistent with the responses of animal tumours and of human squamous carcinomas of the cervix uteri, lung and head and neck [1-3]. The data show that as fraction size increases above 2.0 Gy, the ratio of tumours cured to late adverse effects falls, a highly unfavourable relationship. This may not apply to all tumour types, though. The fractionation sensitivity of normal tissues and tumours is well described by a linear-quadratic model [4]. The α/β value in this simple empirical formula (units Gy) is a practical descriptor of the sensitivity to fraction size. Values of α/β in the range 1-6 Gy are typical of late responding tissues, with higher values (≥10 Gy) typical of squamous carcinomas and early responding normal tissues. The hypothesis relevant to the present discussion is that α/β values for breast cancer are closer to those of late normal tissue responses than to human squamous carcinoma. The implication of this hypothesis is that hypofractionation should be evaluated for the treatment of primary breast cancer (the following arguments do not apply to treatment of the lymphatic pathways due to the high fractionation sensitivity of the brachial plexus).

An α/β value in the range 4-5 Gy was first estimated for the response of locally advanced and recurrent chest wall breast cancer in the early 1950's, and analysed using the linear quadratic model in the mid-1980's [5, 6]. More recently, a direct estimate of 4.1 Gy (95% CI 1.0–9.7) was reported for the fractionation sensitivity of breast cancer in the Royal Marsden Hospital/Gloucestershire Oncology Centre Breast Fractionation Trial (N=1,410) [7]. Meanwhile, a randomised comparison of 50 Gy in 25 fractions of 2.0 Gy and 42.5 Gy in 16 fractions of 2.67 Gy (N=1,234) in Ontario reported no significant differences in local tumour recurrence between arms [8]. If the two Ontario schedules are truly iso-effective with respect to tumour control, it implies an α/β value of 3 Gy (this could be an underestimate if the difference between 5 weeks and 3 weeks treatment time is relevant). Similar fractionation sensitivity, including an α/β value as low as

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1.5 Gy, has recently been suggested for prostate cancer [9].

The UK Standardisation of Radiotherapy (START) Trial is testing the fractionation sensitivity of breast cancer in a design that incorporates two randomisations: Trial A (N=2,236) is an explanatory trial that tests 50 Gy in 25 fractions of 2.0 Gy against two dose levels of a 13-fraction regimen delivering 3.0 Gy or 3.2 Gy fractions over 5 weeks; Trial B (N=2,215) is a pragmatic trial testing 50 Gy in 25 fractions against 40 Gy in 15 fractions of 2.67 Gy. If the relatively high fractionation sensitivity of breast cancer is confirmed (no results have been reported to date), the implications are that larger fraction sizes have no disadvantages, and perhaps significant advantages, for women with primary breast cancer. Since it is unlikely that 13- or 15-fraction schedules would represent the limit of what might be achieved, further studies are justified to test the limits of hypofractionation in breast cancer.

For example, 5 fractions of 5.7 or 6.0 Gy are predicted by the linear quadratic model to be equivalent to 25 fractions of 2.0 Gy, assuming α/β values of 3.0 Gy or 4.0 Gy, respectively [4]. Based on human skin responses, the linear-quadratic model performs reliably over this range of radiation fraction sizes [10, 11]. However, there is limited human experience with once-weekly fractionation in the context of breast cancer radiotherapy. Six fractions of 6.5 Gy over 6 weeks to the whole breast or chest wall using tangential megavoltage fields were evaluated in a series of 84 patients followed up for 36–94 months at Guildford, UK [12]. Acute skin reactions were reportedly mild and only 1/36 patients treated to whole breast developed a severe delayed skin reaction. In a recent French study, 152 women were treated with 5 fractions of 6.5 Gy over 5 weeks with 3 local relapses at a median follow up of >5 years, but no comments on normal tissue responses [13]. Randomised clinical trials are needed to formally test the safety of this approach prior to evaluating efficacy (tumour control) in a large trial. This is the background to the ongoing UK FAST Trial (N=900) that tests 50 Gy in 25 fractions of whole breast radiotherapy against 2 dose levels of a 5-fraction schedule delivered over 5 weeks (5.7 Gy or 6.0 Gy per fraction) using 3D radiation dose compensation. The primary endpoint is late normal tissue response. If the 3-year data are encouraging, a large phase 3 trial will be needed to evaluate local tumour control, quality of life and health economic consequences.

Hypofractionation lends itself to acceleration, taking advantage of the relative sparing of early skin reactions as fraction size increases and the absence of a significant time dependency for late adverse effects. Tumour repopulation has recently been tested as a determinant of treatment outcome in the context of adjuvant systemic therapy. In a randomised comparison of conventional 3-weekly schedules of doxorubicin and cyclophosphamide with the same chemotherapy doses given at 2-weekly intervals (using growth factors to accelerate marrow recovery), the hazard ratios for disease-free and overall survival associated with 2-weekly chemotherapy were 0.74 (p=0.01) and 0.69 (p=0.01), respectively in 2,005 patients [14]. Recent reports of accelerated radiotherapy fractionation in head and neck cancer indicate that very modest shortening of treatment has a detectable impact on local control. In a trial of 1,476 patients randomised to 5 (control arm) or 6 (test arm) fractions per week of conventional radiotherapy, local tumour control in the test arm was 76% patients compared to 64% in the control group [15]. In this study, shortening treatment by only 7 days was associated with a 12% absolute reduction in local recurrence at the primary site, a reduction in the odds of recurrence of 16%. The possible implications for primary breast cancer are that modest reductions in treatment time may translate into worthwhile gains in tumour control without enhanced late normal tissue injuries. If the predicted late adverse effects of once-weekly 5.7-6.0 Gy fraction sizes are confirmed in the current FAST trial, it may justify future evaluation of accelerated hypofractionated radiotherapy.

Finally, the implications of advanced techniques (intensity modulated radiotherapy) for delivering the biological advantages of hypofractionation are worth considering. Rather than increase dose intensity by increasing the number of 2.0 Gy fractions, it creates opportunities for escalating dose intensity by modulating fraction size (this argument does not hold for the lymphatic pathways). Even if the fractionation sensitivity (as expressed by the α/β value) of breast cancer is not quite as great as the normal tissues of the breast, shorter overall treatment times needed to deliver concomitant boost using intensity modulated radiotherapy could be advantageous if tumour proliferation is a significant determinant of local control. The implications of dose escalated intensity modulated radiotherapy are under test in the forthcoming UK IMPORT Trial. The hypothesis is that higher doses per fraction to high-risk areas and lower fraction sizes to low-risk areas of the breast will offer a clinically superior and cost-effective approach of matching dose intensity to tumour recurrence risk compared to standard sequential boost techniques. In conclusion, future prospects for exploiting the biology of hypofractionation in breast cancer using advanced radiotherapy technologies look bright, with prospects for testing a 5-fraction, perhaps even a 5-day, schedule of dose escalated intensity modulated radiotherapy by the end of the decade.

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