Clinics in Oncology

Editorial
Published: 13 Feb, 2017

Hypo Fractionated Radiotherapy in Prostate Cancer

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Editorial

External beam Radiation Therapy (RT) is given in many small fractions (fractionated RT) usually 20-40 with a dose per fraction of 1.8-2 Gy, because it is known that cell-killing is much less compared to a single-dose or few large doses [1-3]. Fractionation spares some of the radiation-induced damage of the normal tissues--surrounding the area of the tumour--which they can recover from, while neoplastic tissues will not, resulting in the cure of cancer with radiotherapy.

The macroscopic and clinical effects of fractionation on neoplastic and normal tissues can be measured with the iso-effective Linear-Quadratic formulation [1-4] which calculates the Biologically Effective Dose of fractionated RT schedules. The basic tissue-related parameter in this formula is the α/β ratio which characterizes each type of tissue [4,5].

Tumours and late-responding normal tissues respond differently in variable RT dose fractionations because of the larger proportion of cycling cells in tumors. Late reacting normal tissues have a lower α/β ratio (2-5 Gy) and therefore a higher fractionation sensitivity compared to the early-reacting normal tissues and most of the tumors (α/β = 8-15 Gy).

The last ones have a high fractionation sensitivity as an increase in the dose per fraction (for a given total dose) causes more cell-kill to them, compared to the cell-kill an equal increase of dose per fraction (for the same total dose) causes to tissues characterized by a high α/β ratio [6] (the interested reader can look at references 1 and 2 and they can also do their own simple calculations using clinical examples).

Prostate tumors contain smaller (than the other cancers)fractions of cycling cells, so after an analysis of the clinical RT data and dose-response relationships, various authors suggested that prostate tumors might not respond to changes in fractionation similarly to other cancers. They are characterized by low α/β ratios and therefore have high-fractionation sensitivity. For prostate cancer α/β ratio has been calculated at 1.5 Gy [7-11] and more recently based on data of modern clinical studies at 1.3 Gy or higher at 1.8 Gy in the CHHIP trial [12-15].

Consequently there is a therapeutic benefit expected if they were treated with fewer and larger fractions—a technique called hypo fractionated RT [6] -- where doses per fraction of 2.5-3.5 Gy are employed. With the recent advancements of technical capacity in RT and the excellent localization, treatment planning and dose delivery techniques (IMRT, IGRT, Tomotherapy) it has been possible to make hypo fractionation feasible and safe (in terms of normal tissue sparing) especially in prostate cancer patients.

The relevant, with the prostate, late-responding normal tissue is the rectum and there is some evidence that α/β ratio of the rectumis around 4 Gy, i.e. higher than for most other late sequelae [16]. As Brenner [7] has noted this would result in increased tumor control for a given level of late complications, or decreased late complications for a given level of tumor control i.e. an increase of therapeutic ratio.

However hypo fractionation for prostate Ca is not an entirely novel treatment approach. Satisfactory outcomes have been reported 22 years' experience (1962–1984) with 232 prostate cancer patients treated with 6-fractions of 6 Gy each with the much inferior dose distributions of that age (compared to the current ones) [17]. There is also extensive experience from the Manchester "hypo fractionation school" of treating prostate cancer with a 15 x 3.1 Gy (total 46.5 Gy) [18].

In the last couple of years, randomized studies (Table 1) comparing standard with hypo fractionated RT schedules in more than 6,000 patients—mainly of low and intermediate-risk—have reported that hypo fractionated RT is working at least equally well with standard fractionation. Of note is that the effect of hypo fractionation remained regardless of the use of hormonotherapy. The urinary and gastrointestinal reactions were comparable and the interested reader should refer

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Received Date: *23 Nov 2016*
Accepted Date: *07 Feb 2017*
Published Date: *13 Feb 2017*

Citation:
Plataniotis G. Hypo Fractionated Radiotherapy in Prostate Cancer. Clin Oncol. 2017; 2: 1201.

Table 1: The recently reported randomised trials on prostate hypo fractionated RT [12-15].

TRIAL	CHHIP trial (12)	PROFIT trial (15)	RTOG 0415 (13)	HYPRO trial (14)
Nm of patients	3216	1206	1092	804
Fractionation—% recurrence rate	2 Gy x 37=74 Gy—88.3% 3 Gy x 20 = 60 Gy—90.6% 3 x 19 = 57 Gy—85.9%	2 Gy x 39 = 78 Gy—79% 3 Gy x 20 = 60 Gy—79%	1.8 x 41 = 73.8 Gy—85% 2.5 Gy x 28 =70Gy---86%	2 Gy x 39 =78 Gy—77% 3.4 Gy x 19 =64 Gy—81%
Hormonotherapy	3–6 months of neoadjuvant and concurrent	No	No	60% concomitant
Median f-up time	62 months	72	69.6	60
Risk group	Low—15% Intermediate---73% High—12%	Intermediate risk	Low-risk	Intermediate and high risk
Recurrence criterion	Biochemical/clinical	Biochemical	Biochemical	Biochemical/clinical

to the original publications [12-15] taking into account the possible differences in RT techniques.

The simultaneous integrated boost technique used in the Intensity Modulated RT (IMRT) involves a dose gradient across the (three in most techniques) Planning Target Volumes (PTVs), and reduces the dose and the dose per fraction by identical proportions and therefore is not expected to be affecting the observed hypo fractionation effect [19].

Following the reported and gained experience it is felt that hypo fractionated RT for the low and intermediate-risk prostate Ca patients can become a standard of care [20], provided that advanced RT techniques are used. This will increase patients' convenience and turnover in RT departments [20].

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