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Are we ready for a paradigm shift from high-dose conventional to moderate hypofractionated radiotherapy in intermediate-high risk prostate cancer? A systematic review of randomized controlled trials with trial sequential analysis

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ABSTRACT

Aim: to evaluate efficacy and late toxicity of moderate hypofractionated (HFRT) over high-dose ($\geq$ 76 Gy) conventional radiotherapy (CRT) in a non-inferiority perspective.
Methods: Randomized controlled trials (RCTs) were included. HFRT regimens were deemed non-inferior to high-dose CRT if the computed CI for the overall RR did not exceed the non-inferiority margin of 7%.
Results: When the prespecified margin, corresponding to a critical RR of 0.930 for CCS, OS and BFS, was used all efficacy outcomes satisfied the criteria for the non-inferiority analysis indicating the non-inferiority of HFRT regimens over high-dose CRT in the medium term period. Differently, the evidence concerning the late toxicity was inconclusive.
Conclusions: Noninferiority analysis indicates that moderate HFRT regimes are non-inferior over high-dose CRT in the medium-term. Inconclusive is the evidence for the late toxicity. Longer follow-up will provide a more clear answer concerning the non-inferiority of HFRT regimens in the long-term period.

1. Introduction

In the past two decades hypofractionated radiation (HFRT) regimes have been extensively explored in the management of localized Pca both in retrospective, prospective (Valeriani et al., 2018; Di Staso et al., 2010; Tombolini et al., 2010; Adkison et al., 2012; Valeriani et al., 2014; Pervez et al., 2010; Zilli et al., 2014; Hegazy et al., 2016; Lim et al., 2008; Quon et al., 2012) and randomized trials (RCTs) (Lee et al., 2016; Lukka et al., 2005; Aluwini et al., 2016; Catton et al., 2017; Incrocci et al., 2016; Dearnaley et al., 2016, 2012; Pollack et al., 2013; Shaikh et al., 2015; Yeoh et al., 2011; Kuban et al., 2010; Hoffman et al., 2014; Anon, 2019; Arcangeli et al., 2017). The rationale for treating Pca with hypofractionated regimens is based on the expected improved therapeutic index with respect to conventional regimens (Höcht et al., 2017a). At the same time, a number of additional advantages are conferred to hypofractionation mainly in terms of resource allocation considerations (Höcht et al., 2017a). However, although these advantages may be considered as added bonuses, the primary goal of these alterated fractionation regimens should be an improved efficacy with respect to conventional regimens with equivalence in short and long-term toxicity. In this regard, a number of trials have been conducted with the aim to obtain a therapeutic gain or alternatively an

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almost equivalence with respect to conventional fractionations both in terms of efficacy and toxicity (Lee et al., 2016; Lukka et al., 2005; Aluwini et al., 2016; Catton et al., 2017; Incrocci et al., 2016; Dearnaley et al., 2016, 2012; Pollack et al., 2013; Shaikh et al., 2015; Yeoh et al., 2011; Kuban et al., 2010; Hoffman et al., 2014; Anon, 2019; Arcangeli et al., 2017). A significant heterogeneity in fractionation and cumulative dose for both moderate hypofractionated and conventional regimens has been reported in literature (Valeriani et al., 2018; Di Staso et al., 2010; Tombolini et al., 2010; Adkison et al., 2012; Valeriani et al., 2014; Pervez et al., 2010; Zilli et al., 2014; Hegazy et al., 2016; Lim et al., 2008; Quon et al., 2012; Lee et al., 2016; Lukka et al., 2005; Aluwini et al., 2016; Catton et al., 2017; Incrocci et al., 2016; Dearnaley et al., 2016, 2012; Pollack et al., 2013; Shaikh et al., 2015; Yeoh et al., 2011; Kuban et al., 2010; Hoffman et al., 2014; Anon, 2019; Arcangeli et al., 2017; Höcht et al., 2017a). In head to head RCTs hypofractionated regimens were in the range of 52.5–72 Gy while conventional regimens were in the range of 64–80 Gy (Lee et al., 2016; Lukka et al., 2005; Aluwini et al., 2016; Catton et al., 2017; Incrocci et al., 2016; Dearnaley et al., 2016, 2012; Pollack et al., 2013; Shaikh et al., 2015; Yeoh et al., 2011; Kuban et al., 2010; Hoffman et al., 2014; Anon, 2019; Arcangeli et al., 2017). This dose heterogeneity may have a significant impact on the comparability across the trials and, importantly, the use of cumulative dose below 74 Gy in conventionally fractionated arms, especially in men with intermediate and high risk Pca, may overestimate both the hypofractionated regimens efficacy and toxicity. In this regard, a grounding body of evidence has consistently suggested that conventionally fractionated dose-escalated regimens can be prescribed to the prostate gland improving the biochemical free survival (BFS) as compared with lower cumulative dose (Hou et al., 2015). However, dose-escalated regimens produced an increased incidence of late toxicity (Hou et al., 2015). To date, any evidence concerning the non-inferiority of moderate HFRT versus high-dose conventional regimens in men with intermediate and high-risk Pca was present in literature. So, this systematic review was aimed to evaluate the efficacy and late toxicity of moderate HFRT over high-dose ($\geq$ 76 Gy) conventional radiotherapy (CRT) in a non-inferiority perspective and using a Trial Sequential Analysis approach. This choice of this specific clinical scenario was based on the considerations that doses of 76 Gy or greater more closely approximate the current standards for the treatment of intermediate and high risk Pca.

2. Materials and methods

2.1. Search strategy and study selection

The study inclusion criteria were RCTs involving patients with localized intermediate and high-risk PCa and treated with moderately hypofractionated regimens (HRT) or high-dose CRT. High-dose CRT was defined as a cumulative dose of 76 Gy or greater delivered in conventional fractionations. A minimum follow-up period of 5 years was required for the assessment of the efficacy outcomes. The treatment volumes had to be the same for both arms and had to include the whole prostate, with or without the seminal vesicles or pelvic lymph nodes. RCTs enrolling men treated with androgen deprivation therapy (ADT) were included, provided that the treatments had to be the same for both arms to avoid confounding. All RCTs using dose per fraction greater than 4 Gy were excluded. This arbitrary definition was based on the current literature which defines moderate hypofractionation a dose per fraction in the range of 2.5–4.0 Gy which are usually delivered in at least 4–6 weeks (Brenner and Hall, 2018; Benjamin et al., 2017; Dearnaley and Hall, 2017; Höcht et al., 2017b; Royce et al., 2017). Studies were eligible irrespective of whether image guidance or IMRT or 3DCRT was used to deliver the radiation treatment. Studies were excluded if essential information was missing and could not be obtained from the authors. Trials using brachytherapy as sole modality or as a boost were excluded. The literature search was performed on January 2019 and included the trials indexed in the MEDLINE database. The flow diagram for the literature selection process was reported in Fig. 1.

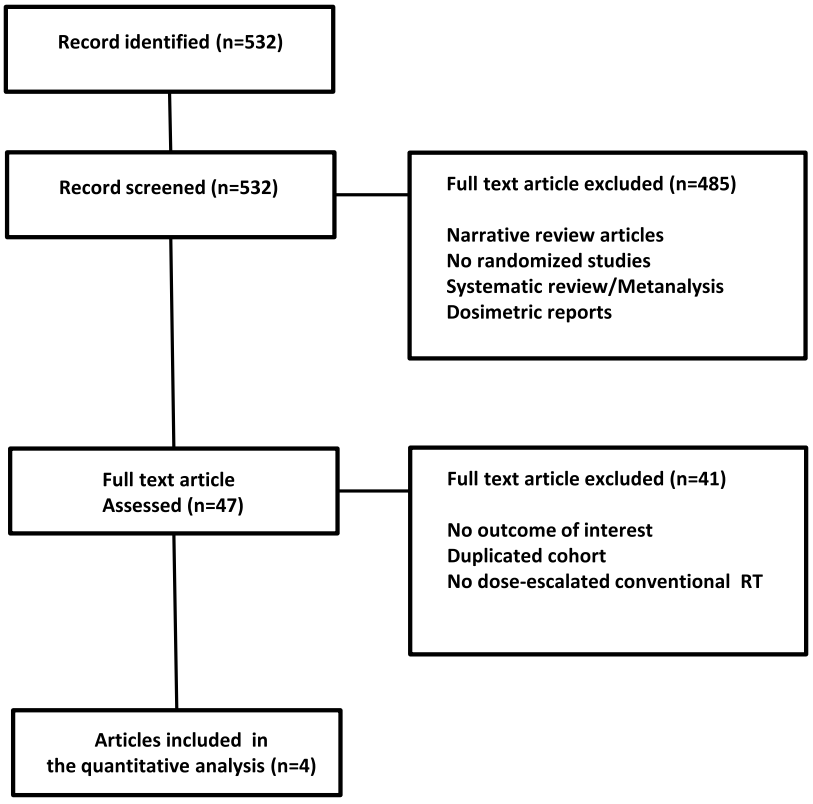

Fig. 1. Flow diagram for the literature selection process.

The initial selection was based on titles and abstracts. The full text copies of relevant publications were screened independently by two reviewers (GLG, FL), with all discrepancies resolved through discussion with a third reviewer (VT). Additional articles and abstracts were retrieved manually after scrutinizing the reference lists of the screened publications. All references were downloaded for consolidation and elimination of duplicates. The following Medical Subject Headings (MeSH) keywords were used for the literature search: MEDLINE Search strategy ("prostatic neoplasms"[MeSH Terms] OR ("prostatic"[All Fields] AND "neoplasms"[All Fields]) OR "prostatic neoplasms"[All Fields] OR ("prostate"[All Fields] AND "cancer"[All Fields]) OR "prostate cancer"[All Fields]) AND ("radiotherapy"[Subheading] OR "radiotherapy"[All Fields] OR "radiotherapy"[MeSH Terms]) AND hypofractionated[All Fields] AND ("clinical trial"[Publication Type] OR "clinical trials as topic"[MeSH Terms] OR "clinical trial"[All Fields]). A total of 532 records were identified and 47 of them were subjected to a full text review. These reports were assessed for their suitability according to the pre-specified inclusion criteria. Four RCTs (Aluwini et al., 2016; Catton et al., 2017; Incrocci et al., 2016; Pollack et al., 2013; Arcangeli et al., 2017) met the inclusion criteria and were used to generate evidence for this systematic review. The study characteristics of the included trails are reported in Table 1.

2.2. Outcome measures

2.2.1. Primary endpoints

Assessment of non-inferiority of HFRT regimens over high-dose CRT in terms of:

a Cancer-Specific Survival (CSS)
b Overall Survival (OS)
c Biochemical Free Survival (BFS)

2.2.2. Secondary endpoints

Assessment of non-inferiority of HFRT regimens over high-dose CRT in terms of:

a Late $\geq$ Grade 2 GU and GI toxicity.

2.3. Criteria for the non-inferiority conclusiveness

In our metanalysis HFRT treatment was deemed non-inferior to the reference treatment (high-dose CRT) or inconclusive if the computed CI for the overall RR for both efficacy and toxicity parameters does not exceed the non-inferiority margin or if they crossed the margin of non-inferiority (Althunian et al., 2017). In this systematic review the non-inferiority margin of 7% in RR was adopted. The selection of this non-inferiority margin was based upon the current literature and it was in the range of that adopted in the RCTs comparing conventional and hypofractionated radiotherapy (Catton et al., 2017; Incrocci et al., 2016; Dearnaley et al., 2016, 2012). The assessment of metanalysis conclusiveness was also performed by the use of the Trial Sequential Analysis (TSA).

2.4. Statistical analysis

The Relative Risk (RR) with 95% Confidence Interval (CI) was used as effect measure of this systematic review. This measure has the merit to provide more conservative evidence. An intention-to-treat analysis (ITT) was used in this systematic review. For meta-analyses with a low number of included trials, the Empirical Bayes binary random effect was used since it is usually more generalizable to a wide range of scenarios than fixed effect. Trial sequential analysis (TSA) was used in this systematic review in order to assess if evidence drawn can be considered statistically definitive or if additional trials have to be conducted. The TSA monitoring boundaries were constructed using the Lan-DeMets alpha-spending approach corresponding to the O'Brien-Fleming boundaries. We conducted TSA with the intention of maintaining an overall 5% risk of a type I error. The incidence of control group (CRT arm) outcome measures was defined according to the included trials at low risk of bias. This margin was also used to conduct the trial sequential analysis. TSA was carried out by TSA viewer software version 0.9 Beta (Copenhagen Trial unit, 2011). All statistical analyses were also carried out by OpenMEE software developed at the Center for Evidence-based Medicine of Brown University (Box G-S121-8, School of Public Health, Providence, RI 02912) and available at http://www.cebm.brown.edu/open_mee.

3. Results

3.1. Demographics and baseline characteristics

A total of 2481 men were enrolled in the four RCTs included in this systematic review (Aluwini et al., 2016; Catton et al., 2017; Incrocci et al., 2016; Pollack et al., 2013; Arcangeli et al., 2017) with 1249 men receiving HFRT and 1232 receiving high-dose CRT, respectively (p = 0.87). Overall, the vast majority of the study cohorts was composed of men with intermediate (63.7%; 1594/2481) or high-risk (34.3%; 857/2481) PCa. Men with low risk PCa were the remaining 2% (46/2481). The percentage of men receiving androgen deprivation

Table 1
Clinical and dosimetric characteristics of included trails.

Trial	Enrolled Subjects (n)	Risk Group (%)	T stage	GS	ADT (%)	Techniques	Arms					
							HFRT			CRT		
							Dose (Gy)	*Gy/Fx (Gy)*	*$EQD_{2\ Gy}$ $BED_{1,5Gy}$*	*Dose (Gy)*	*Gy/Fx*	*$EQD_{2\ Gy}$ $BED_{1,5Gy}$*
PROFIT	1206	I = 100	T1-T2	$\leq$7	5,5	3DCRT/IMRT IGRT	60,0	3,0	77,14/ 180	78,0	2,0	78,0/ 182
IRE	168	H = 100	T1-T3	$\leq$10	100	3DCRT No IGRT	62,0	3,1	81,49/ 190,13	80,0	2,0	80,0/ 186,7
HYPRO	804	I = 26,5 H = 73,5	T1-T4	$\leq$10	66,8	IMRT IGRT	64,6	3,4	90.44/ 211,03	78,0	2,0	78,0/ 182
FCCC	303	L = 15,2 I = 56,4 H = 28,4	T1-T3	$\leq$10	45,8	IMRT IGRT	70,2	2,7	84,24/ 196,56	76,0	2,0	76,0/ 177,33

I = Intermediate; L = Low; H= High; ADT = Androgen Deprivation Therapy; HFRT= Hypofractionated Radiotherapy; CRT = Conventional Radiotherapy; GS = Gleason Score; BED = Biologically Effective Dose; EQD_2 = Equivalent dose in 2 Gy fractions; IMRT = Intensity-modulated radiotherapy; IGRT = Image-guided radiation therapy; Fx = Fraction.

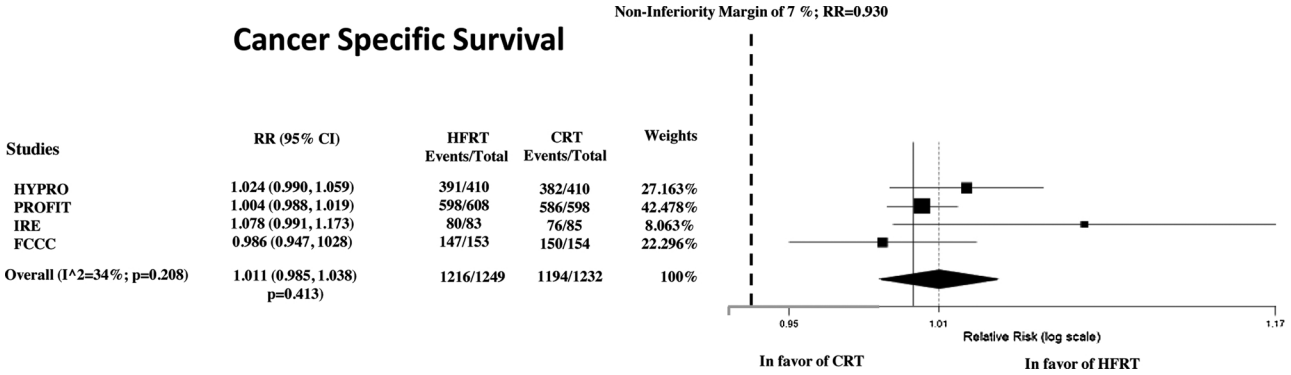

Fig. 2. Forest plot showing the comparative effect in Cancer specific survival of HFRT against high-dose CRT.

therapy (ADT) was 37.4% (935/2481) and the T stage ranged from T1 to T4. All Gleason scores were included and the pre-RT PSA was below 100 ng/mL. Four different hypofractionated regimens were used with dose per fraction ranging from 2.7 Gy to 3.4 Gy Gy. The total doses reported in the conventional radiation treatments ranged from 76 Gy to 80 Gy delivered at 2 Gy per daily dose. PTVs included the whole prostate, with or without the seminal vesicles and pelvic lymph nodes. The most common ADT regimen was LH-RH analogue. Table 1 lists some of the clinical and dosimetric variables of the included RCTs.

3.2. Oncological outcomes after radiation treatment

When the oncological performances of the radiation regimens were analyzed, HFRT regimens did not perform significantly better than dose-escalated CRT in terms of CSS (RR 1.011; 95% CI, 0.985–1.035; p = 0.413) (Fig. 2) (2481 randomized subjects). Even when the OS was used as the oncological endpoint, HFRT regimens did not perform significantly better than dose-escalated conventional regimens (RR 1.008; 95% CI, 0.976–1.049; p = 0.637) (Fig. 3) (2481 randomized subjects). When the treatment regimens were compared in terms of BFS, HFRT regimens did not perform significantly better than dose-escalated conventional regimens (RR 1.024; 95% CI, 0.985, 1.065; p = 0.231) (Fig. 4) (2481 randomized subjects). Similarly, no significant difference in the rate of men with biochemical recurrence at the last follow-up was found for men treated with HFRT and CRT (RR 1.024; 95% CI, 0.985–1.065; p = 0.231). For the non-inferiority analysis we assumed, in the conventionally fractionated arm, the cumulative rate in the efficacy parameters found in our metanalysis in order to exclude a decrease of 7% with respect to hypofractionated arm. This non-inferiority margin corresponded to a critical RR of 0.930 for CCS, OS and BFS, respectively. These critical RRs were used for the non-inferiority analyses. As reported in the Figs. 2–4, the computed CIs for the overall RR were in the range of 0.985–1.038 for the CSS, 0.976–1.040 for the OS and 0.985–1.065 for the BFS. All these three oncological outcomes satisfied the criterion for the non-inferiority analysis since the lower CIs does not exceed the pre-specified margins indicating the non-inferiority of HFRT regimens over high-dose CRT.

3.3. Late genitourinary and gastrointestinal toxicity

When the late GU and GI toxicity was compared in terms of RR, HFRT regimens did not perform significantly worse than high-dose conventional regimens (Late GU toxicity; RR 1.000 ; 95% CI, 0.895–1.118; p = 0.998) (Fig. 5) (Late GI toxicity; RR 0.908; 95% CI, 0.662–1.244; p = 0.545) (Fig. 6) (2481 randomized subjects). The non-inferiority margin of 7% corresponded to critical a RR of 0.930 for late GU and GI toxicity. As reported in Figs. 5 and 6, the computed CIs for the overall RRs were in the range of 0.895–1.118 for late GU toxicity and of 0.662–1.244 for late GI toxicity. The analysis of the CIs boundaries of the computed RRs indicated that they exceeded the pre-specified margin indicating that the evidence concerning the non-inferiority of HFRT regimens over high dose CRT was inconclusive. Since from the forest plot showing late GI toxicity was evident that the significant heterogeneity (I^2 = 68%; p = 0.014) found was imputable to the HYPRO trial (Fig. 6) an analysis excluding this study was performed in order to investigate if the evidence concerning the late toxicity remained inconclusive. After excluding this trial no residual heterogeneity (I^2 = 0%; p = 0.446) was observed but the evidence on the late GI toxicity remained inconclusive since the upper CI (0.937) of estimated RR computed in our systematic review crossed the pre-specified non-inferiority margin (RR = 0.930).

3.4. Trial sequential analysis for the determination of conclusiveness of non-inferiority of HFRT versus high-dose CRT regimens

We deemed our meta-analysis conclusive, in demonstrating that HRFT regimens were non-inferior over high-dose CRT, when the required sample size is reached and the cumulative Z-curves cross the

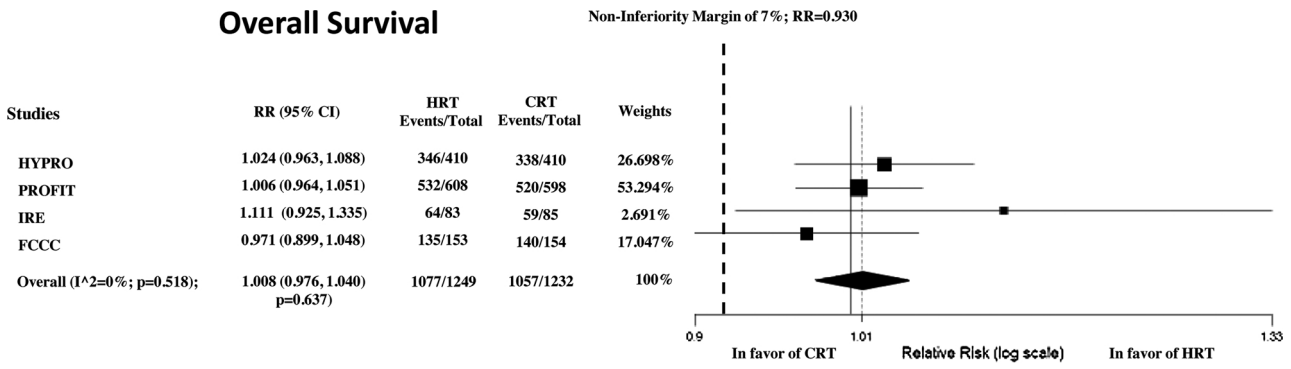

Fig. 3. Forest plot showing the comparative effect in Overall survival of HFRT against high-dose CRT.

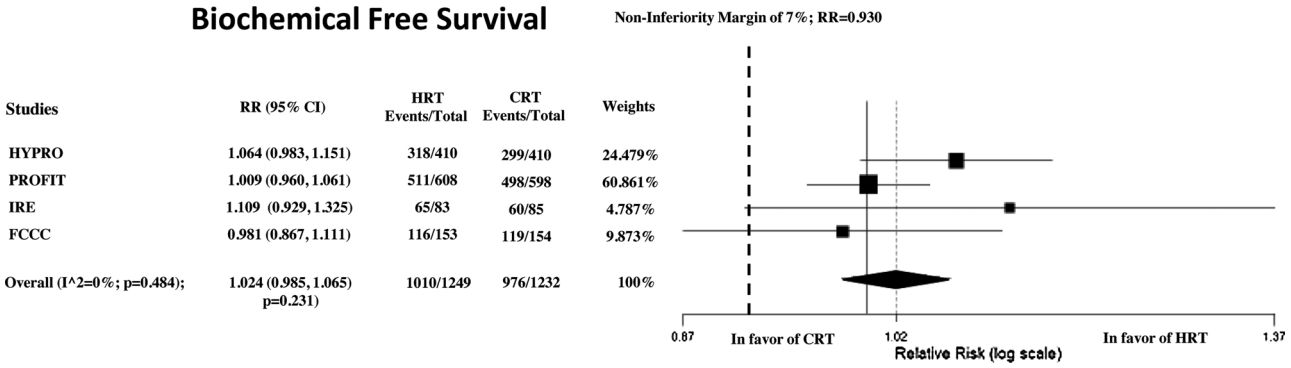

Fig. 4. Forest plot showing the comparative effect in Biochemical Free Survival of HFRT against high-dose CRT.

futility boundaries constructed by TSA. When these two conditions are satisfied a sufficient amount of evidence for the prespecified intervention effect has been reached (Wetterslev et al., 2009). The required sample size assessment was based on the following parameters: alpha error 5%, a beta error 0.20–0.10 (study power in the range of 80%–90%) and non-inferiority margin 7%. TSA analysis indicated that the accrued sample size (2481 patients) exceeded the required sample size (2007 patients for OS, 2464 patients for CSS and 2416 patients for BFS) need to confirm the non-inferiority of HFRT regimens in terms of efficacy parameters (Fig. 6). The TSA analysis on the toxicity parameters was not performed since the criteria for the non-inferiority analysis was not satisfied and no conclusive evidence can be drawn (Fig. 7).

4. Discussion

Over the recent years a number of research groups have explored the topic concerning the comparative efficacy and toxicity of moderate HFRT versus CRT regimens obtaining conflicting evidence (Sun et al., 2014; Royce et al., 2017; Cao et al., 2017; Botrel et al., 2013; Datta et al., 2017). Sun et al. (2014) conducted a meta-analysis assessing the survival outcomes in men with Pca and treated with moderate HFRT or CRT. A better BFS for men treated with HFRT compared with CRT was found with no effect on overall survival, prostate cancer-specific survival and late toxicity. A key limitation of this study was that the evidence was obtained from RCTs and cohort or retrospective studies (Sun et al., 2014). Royce and colleagues Royce et al. (2017) conducted a systematic review on a study population of men with intermediate risk Pca. Only non-inferiority RCTs using moderate hypofractionated fractionations with similar schedules were selected. With these very restrictive inclusion criteria three RCTs were included. They found that HFRT improved DFS, as compared with CRT, with a significant increase in the late GU toxicity in the hypofractionated group. Of the 5484 men included in this analysis, 4278 (78%) received a conventional cumulative dose in the range of 73.8–74 Gy. This dose, in men with intermediate-risk Pca, may be regarded somewhat suboptimal in terms of tumor control and improved DFS. The increased late GU toxicity found with HFRT regimens might be, at least partly, overestimated since data derived from RCTs comparing dose-escalated versus conventional cumulative dose suggested increased GU toxicity in the dose escalated treatments (Hou et al., 2015). Similarly to Royce and colleagues, Cao and co-workers found a better BFS and DFS in men treated with HFRT over conventional CRT (Cao et al., 2017). These authors did not include the final reports from PROFIT and IRE trials and some inaccuracy in the data used to compute the effect measures was introduced in their metanalysis. In two well conducted metanalysis, Botrel and colleagues (Botrel et al., 2013) and Datta and colleagues (Datta et al., 2017) found that HFRT was not more efficacy than CRT with increased acute GI toxicity (Datta et al., 2017). No difference was found for late GU and GI toxicity (Datta et al., 2017). However no aggregate estimates of the efficacy and toxicity, stratified according to the conventionally fractionated cumulative dose, was provided. In our systematic review and meta-analysis the relationship between high-dose conventional regimens and moderate HFRT was specifically investigated selecting the four large published RCTs using conventional cumulative dose in the range of 76–80 Gy. To the best of our knowledge, this represents the first attempt to systematically review this understudied topic. Our study population included individuals with intermediate (63.7%) and high-risk (34.3%) PCa, T1-T4 stages, all Gleason scores and pre-RT PSA $<$ 100 ng/mL. This population includes the subgroup of men with prognostic factors that poses significant therapeutic challenges to radiation oncologists and for which a dose-escalated conventional regimen may be adopted to improve the local tumor control (Hou et al., 2015). The main clinical evidence found in our review is that HFRT regimens are non-inferior over high-dose CRT in terms of OS, CSS and BFS in the medium-term. Noninferiority trials are used to assess whether the effect of a new treatment is not worse than the current standard by more than a noninferiority margin (Mauri

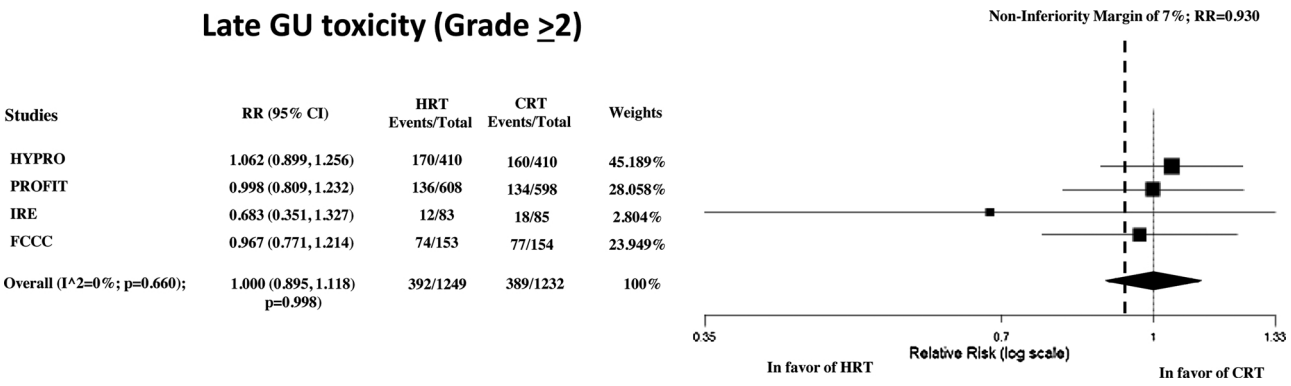

Fig. 5. Forest plot showing the comparative effect in Late GU toxicity (Grade ≥ 2) of HFRT against high-dose CRT.

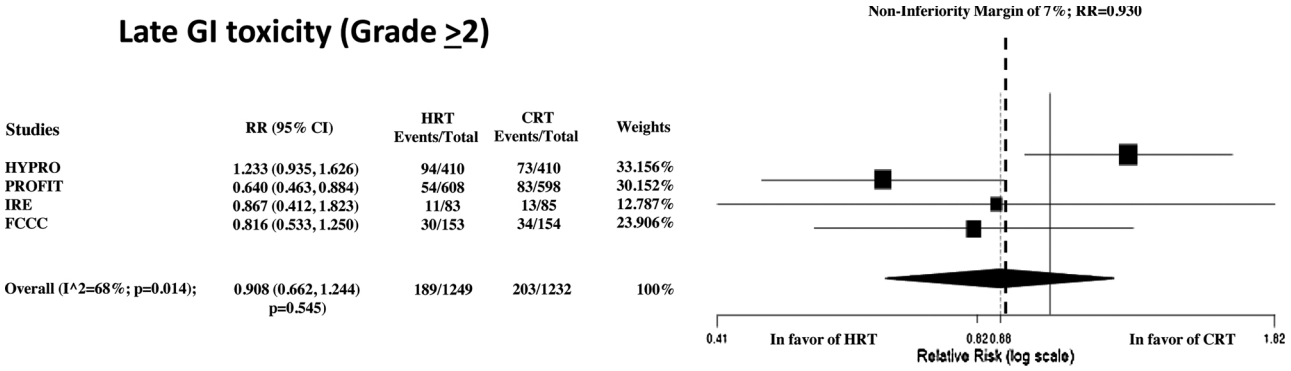

Fig. 6. Forest plot showing the comparative effect in Late GI toxicity (Grade ≥ 2) of HFRT against high-dose CRT.

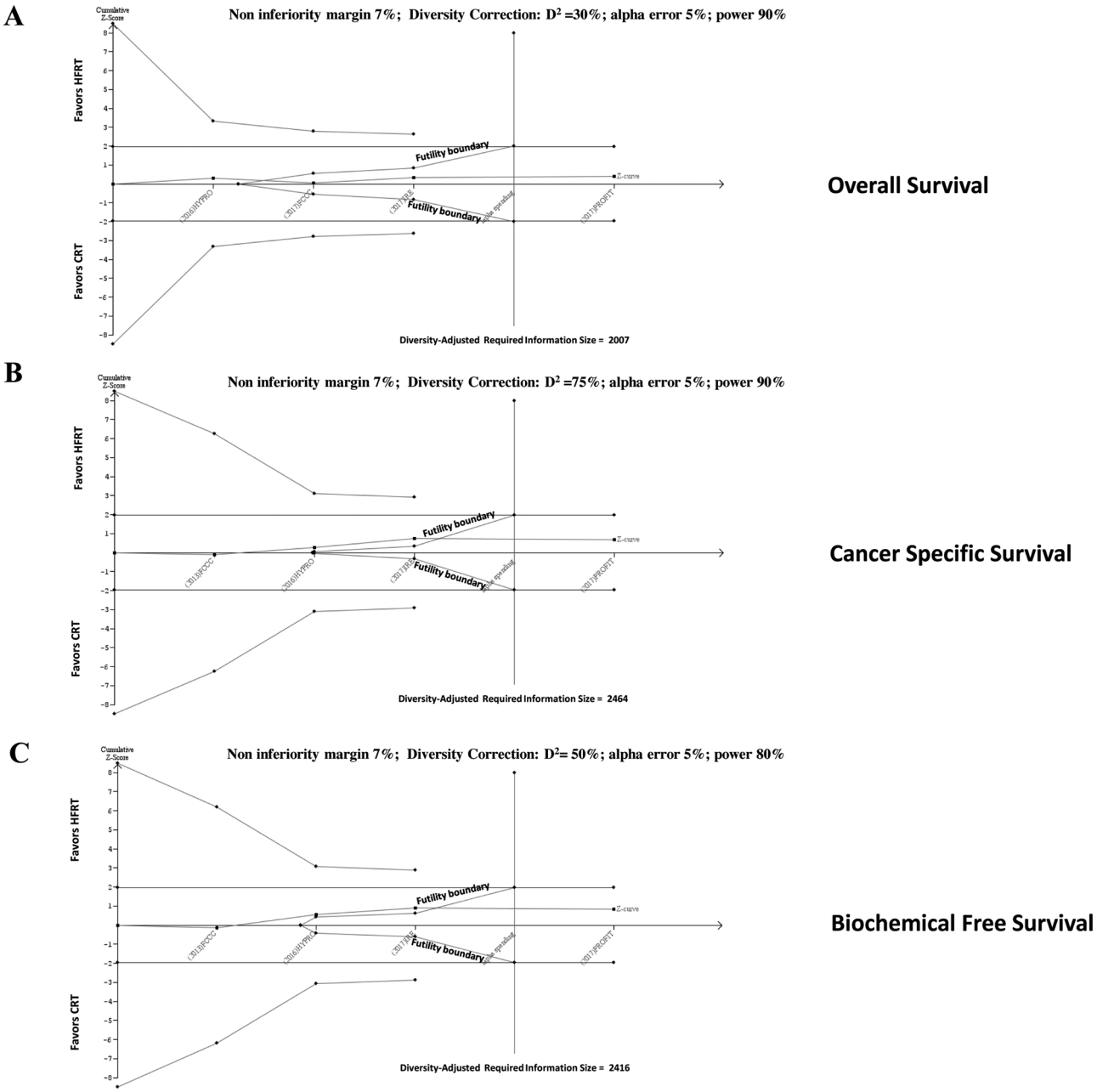

Fig. 7. Trial sequential analyses showing the (A) comparative effect in Overall survival of HFRT against high-dose CRT; (B) comparative effect in Cancer specific survival of HFRT against high-dose CRT; (C) comparative effect in Biochemical Free Survival of HFRT against high-dose CRT.

and D'Agostino, 2018, 2017). Since our evidence was mainly based on RCTs with a non-inferiority study design, strict methodological criteria for the judgment of noninferiority were employed. The simple identification of a statistically significant difference between groups ($P < 0.05$) or a lack of significant difference ($P > 0.05$) by conventional statistical tests is methodologically unfit in this research context since none of these two approaches provides answers about equivalence or noninferiority (Mauri and D'Agostino, 2018, 2017). A more rigorous methodological approach employs a strategy based on the confidence intervals analysis, where equivalence or noninferiority is concluded when the CIs of the statistical measures used to quantify the effects of a new treatment does not exceed the prespecified non-inferiority margin with respect to the outcomes of the current standards (Mauri and D'Agostino, 2018, 2017). When the evidence is interpreted in the light of this approach, the non-inferiority of the HFRT versus high-dose CRT regimens was concluded since the 95% CIs of the overall RRs computed in our metanalysis lie within the 7% margin adopted in our systematic review. The conclusions concerning the non-inferiority of HFRT regimens versus high-dose CRT were corroborated by TSA. The use of this powerful statistical analysis is an absolute novelty in the radiation oncology field. From a statistical point of view, the TSA showed that the cumulative population enrolled in the four trials included in our metanalysis exceeded the sample size required to make our metanalysis conclusive. In addition, the cumulative Z-curves crossed the futility boundaries confirming that HFRT regimens were not inferior to high-dose CRT within the pre-specified margin of 7%. Differently, although HFRT and high-dose CRT regimens seems to have similar late GU and GI toxicity with no significant difference between the two treatment approaches, the 95% CIs of the overall RRs lie out of the 7% of non-inferiority margin suggesting that the evidence concerning the late GU and GI toxicity may be regarded as inconclusive and the non-inferiority of the HFRT versus high-dose CRT cannot be concluded. Obviously, this evidence has important implications for the radiation oncologists community since a number of research groups sustained the use of moderate HFRT as an alternative to conventional treatment regimens basing these recommendations also on toxicity related data. We believe that recommendations on the use of moderate HFRT, based on the toxicity related considerations, should be made with more caution and awareness at least in men with intermediate or high risk Pca and treated with the fractionations used in the four included RCTs.

What lesson can be learned from our analysis? From a statistical point of view our data seem to indicate that HFRT regimens work well as high-dose CRT. This evidence was further confirmed by TSA which indicates that the sample size required to obtain a statistical power sufficient to make conclusive our metanalysis has been obtained. Inconclusive are the evidence concerning the late toxicity profiles. If the findings concerning efficacy are really good news, a main question remains. Are these findings enough to really force a paradigm shift from conventional to moderate hypofractionation regimens in the radiation treatment of Pca in men with intermediate or high risk Pca? Probably not yet. We have to wait more time to have solid evidence in the long-term follow-up for the efficacy and toxicity measures. From a clinical point of view the scenario is more complex and some certainties seems to be less convincing. If it is true that our sophisticated statistical analysis suggests the non-inferiority of HFRT regimens versus high-dose CRT, it is also true that it was obtained from clinical data collected at 5-years of follow-up. This follow-up period is a long-term estimate for many oncological diseases but it has to be considered, at the best, as a middle-term estimate for men with localized Pca. So, longer follow-up will be probably necessary and at least 10-years of clinical results will be required to provide more reliable findings both for efficacy and toxicity parameters. Additional uncertainty, in considering HFRT regimens a valuable alternative to high-dose CRT, is related with the lack of clinical data on what is the most effective hypofractionated fractionation to be used in the current clinical practice. Indirect evidence (Arcangeli et al., 2018) suggests that fractionation regimens lying above or below the isolevel curves for freedom from biochemical failure or toxicity are expected to produce the optimal therapeutic ratio. However, no empirical evidence has been published in head to head RCTs and, in the current practice, no clear recommendation can be provided to radiation practitioners.

5. Conclusions

The evidence here provided suggests that a significant uncertainty exists on the real comparability of moderate HFRT regimens over high-dose CRT in men with intermediate and high-risk Pca. Encouraging results were obtained in men treated by moderate HFRT with similar OS, CSS and BFS at a middle-term follow-up. More concerns exist about the HFRT related late GU and GI toxicity as well as on the most effective hypofractionated fractionation to be used in the current clinical practice. Longer follow-up and additional trials will provide more clear answer on these topics of great interest for the radiation oncologists community.

Conflict of interest statement

None.

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