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Toxicity after moderately hypofractionated versus conventionally fractionated prostate radiotherapy: A systematic review and meta-analysis of the current literature

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ABSTRACT

Background: Moderately hypofractionated radiotherapy (RT) currently represents the standard RT approach for all prostate cancer (PCa) risk categories. We performed a systematic review and meta-analysis of available literature, focusing on acute and late genitourinary (GU) and gastrointestinal (GI) adverse events (AEs) of moderate hypofractionation for localized PCa.

Materials and methods: Literature search was performed and two independent reviewers selected the records according to the following Population (P) Intervention (I) Comparator (C) and Outcomes (O) (PICO) question: "In patients affected by localized PCa (P), moderately hypofractionated RT (defined as a treatment schedule providing a single dose per fraction of 3–4.5 Gy) (I) can be considered equivalent to conventionally fractionated RT (C) in terms of G $\geq$ 2 GI and GU acute and late adverse events (O)?". Bias assessment was performed using Cochrane Cochrane Collaboration's Tool for Assessing Risk of Bias.

Results: Thirteen records were identified and a meta-analysis was performed. Risk of acute GI and GU $\geq$ 2 adverse events in the moderately hypofractionated arm was increased by 9.8 % (95 %CI 4.8 %–14.7 %; $I^2 = 57$ %) and 1.5 % (95 % CI -1.5 %-4.4 %; $I^2 = 0$%), respectively.

Discussion: Overall, majority of trials included in our meta-analysis suggested that moderately hypofractionated RT is equivalent, in terms of GI and GU adverse events, to conventional fractionation. Pooled analysis showed a trend to increased GI toxicity after hypofractionated treatment, but this might be related to dose escalation rather than hypofractionation.

1. Background

Moderately hypofractionated radiotherapy (RT) currently represents the standard RT approach for all prostate cancer (PCa) risk categories (Morgan et al., 2018). Advantage of this approach consist in the lower number of fractions delivered. However, the use of moderately hypofractionated RT is largely based on results from trials showing non-inferiority of this treatment schedule if compared to conventional fractionation (Dearnaley et al., 2016; Catton et al., 2017; Lee et al., 2016), while superiority trials often failed to demonstrate a significant advantage of hypofractionation in terms of clinical outcomes (Pollack et al., 2013; Arcangeli et al., 2017; Incrocci et al., 2016). Considering the subtle balance of advantage and risks for patients, this situation prompts careful comparison between these RT approaches. Indeed, reduced

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treatment time should not be considered sufficient to propose moderate hypofractionation as a standard treatment if patients were exposed to potential harm, especially in the absence of a clear oncological benefit. Ethical and methodological considerations induce to assure, with high degree of certainty, the equivalence in terms of toxicity between different treatment schedules. With the purpose of strengthen the reliability about the actual framework and reduce the potential safety concerns, we performed a systematic review and meta-analysis of available literature, focusing on acute and late Genitourinary (GU) and Gastrointestinal (GI) adverse events of moderate hypofractionation for localized PCa.

2. Materials and methods

Literature search was performed on PubMed, Grey literature, Google search and EMBASE. The following query was used: 'prostate cancer'/exp OR 'cancer, prostate' OR 'prostate cancer' OR 'prostate gland cancer' OR 'prostatic cancer') AND ('hypofractionated radiotherapy'/exp OR 'dose hypofractionation' OR 'hypofractionated irradiation' OR 'hypofractionated radiation therapy' OR 'hypofractionated radiation treatment' OR 'hypofractionated radiotherapy' OR 'radiation dose hypofractionation' OR 'radiation hypofractionation') AND 'conventional fractionation' AND ('radiotherapy'/exp OR 'irradiation therapy' OR 'irradiation treatment' OR 'radiation treatment' OR 'radio therapy' OR 'radio treatment' OR 'radiotherapy' OR 'radiotreatment' OR 'therapy, irradiation' OR 'therapy, radiation' OR 'treatment, irradiation' OR 'treatment, radiation' OR 'x radiotherapy' OR 'x ray therapy' OR 'x ray treatment' OR 'x-ray therapy' OR 'fractionated radiotherapy' OR 'radiation therapy') AND ('toxicity'/exp OR 'tissue toxicity' OR 'toxicity' OR 'toxigenicity' OR 'toxic effect').

After the initial search, two independent reviewers (MB and CB) selected the records according to the following Population (P) Intervention (I) Comparator (C) and Outcomes (O) (PICO) question: "In patients affected by localized PCa (P), moderately hypofractionated RT (defined as a treatment schedule providing a single dose per fraction of 3–4.5 Gy) (I) can be considered equivalent to conventionally fractionated RT (C) in terms of G $\geq$ 2 GI and GU acute and late adverse events (O)?

Both randomized and non-randomized studies comparing moderately hypofractionated RT and conventional RT were included in the analysis. Cross-referencing was allowed. Trial testing proton therapy, brachytherapy or treatment schedules providing single dose per fraction $>$ 4.5 or $<$ 3 Gy were excluded from the analysis.

Bias assessment was performed using Cochrane Cochrane Collaboration's Tool for Assessing Risk of Bias (Higgins et al., 2011). The study-specific differences in the proportions of patients who developed acute G$\geq$ 2 GI and GU adverse events between those treated with hypofractionated RT vs. conventional RT (the latter group taken as reference) were pooled into summary proportion differences and corresponding 95 % confidence intervals using random effect meta-analysis models (command *metan* Stata v.14 StataCorp, College Station, TX USA).

In the CHHip trial (Dearnaley et al., 2016), two groups of patients treated with hypofractionated RT (57 Gy, n = 713, or 60 Gy, n = 720) were separately compared to those treated with conventional RT (74 Gy, n = 715). To ensure independence of estimates while avoiding discarding patients, the differences in proportions of G$\geq$2 GI and GU adverse events entered in the main meta-analysis models were calculated by first merging the patients allocated to the two hypofractionated RT study arms into a single group (n = 1433), and comparing this larger hypofractionated RT group to patients allocated in the conventional RT study arm. In order to test the robustness of the results against this approach, sensitivity analyses were then conducted by alternatively entering in the models the difference in proportions of adverse events obtained by comparing the patients in the conventional RT arm to patients in either hypofractionated RT arm.

A similar approach was used for the study by Soete et al. (2006), which included, however, a group of patients treated with hypofractionated RT (56 Gy, n = 36) and two groups of patients treated with conventional RT ($\geq$75 Gy, n = 114, or 70−78 Gy, n = 238). The heterogeneity of differences in proportions between studies was assessed using the I^2 statistics, which quantifies the percentage of variability that is due to actual heterogeneity rather than chance. When I^2 exceeded 50 %, denoting substantial between-estimates heterogeneity, we used meta-regression and subgroup analyses to search study characteristics that could account for part of the observed heterogeneity, and conducted a leave-one-out sensitivity analysis to assess the impact of each single study on the pooled estimate. Pooled analysis for late adverse events was not performed considering the reduced availability of follow up data after 5 years.

3. Results

After duplicates removal, 140 records were selected. Of these, 127 records were excluded because of their design, wrong intervention arm or endpoint. Thirteen records were identified (Dearnaley et al., 2016; Catton et al., 2017; Arcangeli et al., 2017; Soete et al., 2006; Aluwini et al., 2016; Norkus et al., 2013; Karklelyte et al., 2018; Wilkins et al., 2015; Dearnaley et al., 2012; Wilson et al., 2018; Arcangeli et al., 2010, 2011; Viani et al., 2013) (Fig. 1).

However, some of the records referred to the same cohort of patients, and only final results for each of these cohort was included in the pooled analysis (Table 1).

Soete et al. compared early side effects in a cohort of 36 patients treated with 56 Gy in 16 fractions with 352 historical controls treated with conventional fractionation. Results showed a significant increase in G1-G2 early GI and GU side effects after moderately hypofractionated treatment, but no G3−4 adverse events were reported (Soete et al., 2006). Arcangeli et al. randomized 168 patients to receive hypofractionated (62 Gy in 20 fractions) or conventionally fractionated (80 Gy in 40 fractions) three-dimensional conformal RT to the prostate and seminal vesicles. In terms of GI and GU G $\geq$ 2 toxicity, no difference at 3 years was shown (17 and 14 % vs 16 and 11 % in the hypofractionated and conventionaly fractionated arm, respectively). Results were confirmed after a median follow up of 9 years (Arcangeli et al., 2017, 2010; Arcangeli et al., 2011). CHHiP was a multicentre study in which men were randomized to receive hypofractionated (60/57 Gy in 20 /19 fractions) or conventionally fractionated RT (74 Gy in 37 fractions). No significant increase in GI and GU adverse events at 2 years was found in the first report including 457 patients. These data were confirmed at 5 years on a larger cohort of 3216 patients enrolled (Dearnaley et al., 2016; Wilkins et al., 2015; Dearnaley et al., 2012; Wilson et al., 2018). Preliminary results from another randomized trial were published by Norkus in 2013, including 124 patients receiving either 63 Gy in 20 fractions or 76 Gy in 38 fractions. No difference in acute GU and GI toxicity was noticed. This was confirmed in the following analysis of the complete cohort including 221 patients (Norkus et al., 2013; Karklelyte et al., 2018). A Brazilian prospective double arm study including 217 patients was published in 2013. Men were non-randomly allocated to 69 Gy in 23 fractions or 78 Gy in 39 fractions. The two arms of treatment were equivalent in terms of GI and GU toxicity after 3 months of follow up (Viani et al., 2013). Hypro was a non-inferiority trial randomizing 820 patients to receive either 64.6 Gy in 19 fractions or 78 Gy in 39 fractions. After 60 months of follow up, the study failed to demonstrate that hypofractionation was non-inferior for cumulative late GI and GU toxicity, if compared to conventional fractionation, with estimated HR of 1.16 (90 % CI 0.98–1.38) and 1.19 (90 % CI 0.93–1.52) for cumulative incidence of G$\geq$2 late GU or GI toxicity at 3 years, respectively (Aluwini et al., 2016). Catton et al. published a multicenter non-inferiority trial randomizing intermediate-risk PCa patient to 60 Gy in 20 fractions or 78 Gy in 39 fractions. Results did not show differences in terms of G $\geq$ 3 late GI or GU toxicity (Catton et al., 2017). A meta-analysis of these trials was performed, excluding all preliminary publications, and including only

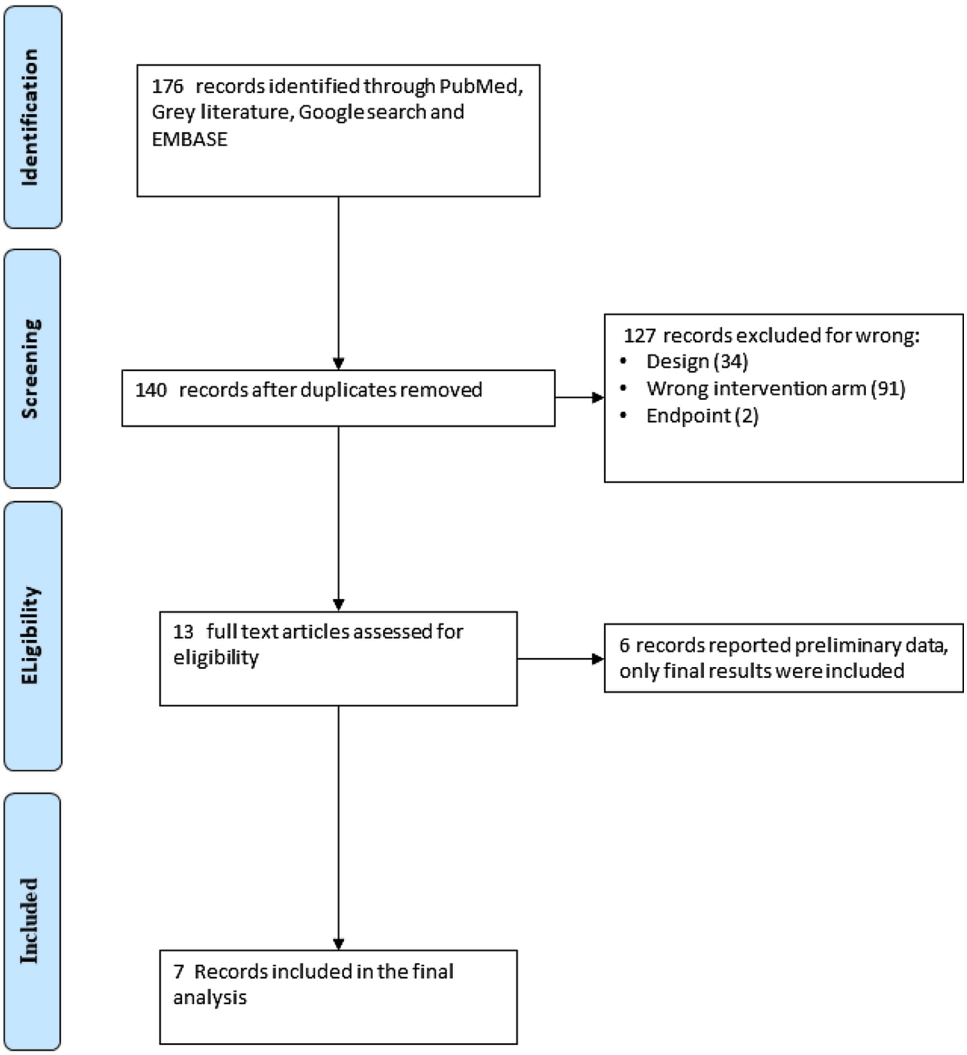

Fig. 1. Consort flow diagram.

final publications from each cohort. Overall, our pooled analysis showed that risk of acute GI and GU $\geq$ 2 adverse events in the moderately hypofractionated arm was increased by 9.8 % (95 %CI 4.8 %–14.7 %; I^2 = 57 %) and 1.5 % (95 % CI -1.5 %-4.4 %; I^2 = 0%), respectively (Figs. 2 and 3). In meta-regression and subgroup analysis, no study characteristic was found to explain a significant share of the between-estimates heterogeneity in the meta-analysis for GI $\geq$ 2 adverse events. Likewise, the removal of one study at a time from the analysis did not drop the I^2 statistics to below 50 %. A sensitivity analysis was performed considering the 60 Gy in 20 fractions or the 57 Gy in 19 fractions cohorts included in the CHHip trial (Dearnaley et al., 2016). Results suggested a 9.8 % (95 % CI 4.7–14.8 %; I^2 = 54.8 %) and 9.6 % (95 % CI 4.8–14.4 %; I^2 = 51.1 %) increase in risk of acute GI $\geq$ 2 toxicity in the two cohorts. Moreover, a 2.2 % (95 % CI -1.0–5.3 %; I^2 = 0.9 %) and 0.9 % (95 % CI -2.3–4.2 %; I^2 = 2.9 %) increase in the risk of acute GU $\geq$2 toxicity was detected. Another sensitivity analysis was performed with patients treated with $\geq$75 Gy in the conventional treatment arm of the trial by Soete et al. (2006). We found a 8.7 % (95 % CI 4.3–13.1 %; I^2 = 41.8 %) and 8.6 % (95 % CI 4.5–12.7 %; I^2 = 34.9 %) increase in terms of acute GI $\geq$ 2 toxicity and a 1.5 % (95 % CI -1.6−4.7%; I^2 = 0.0 %) and 0.2 % (95 % CI -3.0–3.3 %; I^2 = 0.0 %) in terms of acute GU $\geq$ 2 toxicity in the 60 Gy/30 fractions and 57 Gy/19 fractions cohorts, respectively. Results for risk of bias assessment was summarized in Table 2.

High risk of selection bias was detected for Viani et al. (Viani et al., 2013), while Soete et al. study (Soete et al., 2006) was affected by reporting and detection biases. Moreover, follow up for this latter study was not clearly reported, determining further risk of bias.

4. Discussion

Recently published ASTRO, ASCO, and AUA Evidence-Based Guidelines reported no difference between moderate hypofractionation and conventionally fractionated RT in terms of acute and late GU side effects and late GI toxicity, while suggesting to counsel patients about the small increased risk of acute GI toxicity related to moderate hypofractionation (Morgan et al., 2018).

In our study, considering the evidence collected, the vast majority of trials suggested the equivalence, in terms of G $\geq$ 2 GI and GU toxicity, of moderately hypofractionated and conventionally fractionated RT. The only evidence of increased toxicity comes from a non-randomized comparison including only 36 patients (Soete et al., 2006) and from the Hypro trial, failing to show non-inferiority of intervention arm. However, in the second case, the trial was initially powered to show a 10 % reduction in relapse-free survival. Furthermore, the hypofractionated schedule tested corresponded to a slightly higher isoeffective dose if compared to conventional arm (82.7 vs 78 Gy with an alfa/beta of 3) (Aluwini et al., 2016). Of course, mature data about toxicity rate after 5 years are needed to have a reliable assessment about late toxicity comparison. Data from the pooled analysis may raise concern about the 9.8 % acute GI toxicity increase after moderate hypofractionation.

Table 1
Summary of principal results of included trials.

	Study design	N patients	Arms of treatment	Acute GI toxicity	Acute GU toxicity	Late GI toxicity	Late GU toxicity
CHHiP trial*	Randomized	3216	−74 Gy/32 fr.-60 Gy/30 fr.-57 Gy/19 fr.	G≥2 −25% in the 74 Gy group, −38% in the 60 Gy *(p < 0.0001)* −38% in the 57 Gy group *(p < 0.0001)*	G≥2 −46%in the 74 Gy group −49% in the 60 Gy group *(p = 0.34)* −46% in the 57 Gy group *(p = 0.90)*	G≥2 −4% in the 74 Gy group −3% in the 60 Gy group *(p = 0.0075)* −2% in the 57 Gy group *(p = 0.31)*	G≥2 −1% in the 74 Gy group −2% in the 60 Gy *(p = 0.71)* −1% in the 57 Gy group *(p = 0.68)*
Arcangeli et al., 2017	Randomized	168	−80 Gy/40 fr −62 Gy/ 20 fr	G≥2 −21% in the 80 Gy group −35% in the 62 Gy group *(p = .07)*	G≥2 - 40% - 47% *(p = 0.45)*	G≥2 −15.4% in the 80 Gy group −13.5%in the 62 Gy group *(p = 0.57)*	G > 2 −21% in the 80 Gy group −14% in the 62 Gy group *(p = 0.68)*
Catton et al., 2017	Randomized	1206	−78 Gy/39 fr −60 Gy/20 fr	G≥2 −10.4% in the 78 Gy group −16.3% in the 60 Gy group *(P = .003)*	G≥2 −30.6% in the 78 Gy group −30.4% in the 60 Gy group *(p = Non significant)*	G≥2 −2.8% in the 78 Gy group −1.5% in the 60 Gy group *(p = 0.006)*	G≥2 −3% in the 78 Gy group −2.1% in the 60 Gy group *(p = Non significant)*
Norkus et al., 2013	Randomized	124	−76 Gy/38 fr −63 Gy/20 fr	G≥2 −40% in the 76 Gy group −39% in the 63 Gy group *(p = Non significant)*	G≥2 −28% in the 76 Gy group −23% in the 63 Gy group *(p = Non significant)*	G≥2 NR	G≥2 NR
Karklelyte et al., 2018	Randomized	221	−76 Gy/38 fr −63 Gy/20 fr	G≥2 −38% in the 76 Gy group −51% in the 63 Gy group *(p = Non significant)*	G≥2 −32% in the 76 Gy group −33% in the 63 group *(p = Non significant)*	G≥2 NR	G≥2 NR
Viani et al., 2013	Observational	217	−78 Gy/39 fr −69 Gy/ 23 fr	G≥2 −17.2% in the 78 Gy group −20.5% in the 69 Gy group *(p = Non significant)*	G≥2 −20.9% in the 78 Gy group −23.2% in the 69 Gy group *(p = Non significant)*	G≥2 NR	G≥2 NR
Soete et al., 2006	Observational	274	−70–78 Gy/35-27 fr −56 Gy/16 fr	G > 2 - 6–29% in the 70-78 Gy group −36% in the 56 Gy group *(P < 0.01)*	G > 2 - 16–44% in the 70-78 Gy group −44% in the 56 Gy group *(P < 0.01)*	G≥2 NR	G≥2 NR

Note: *further details about radio-biologic modeling resulting from CHHiP data are provided as estimates alpha/beta ratios for individual late rectal toxicity endpoints, for a detailed discussion see Brand et al (Brand et al., 2021).

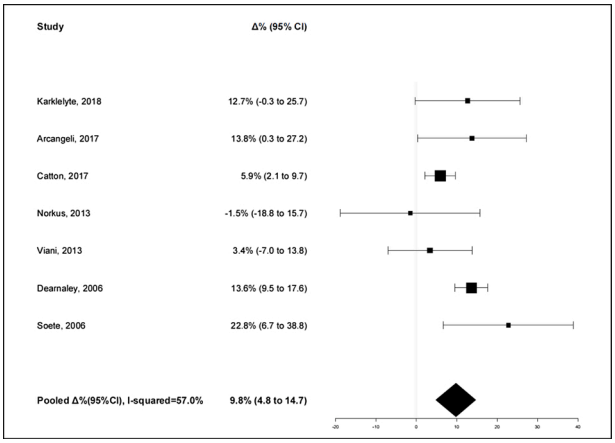

Fig. 2. Pooled analysis of risk of acute gastro-intestinal (GI) toxicity after conventionally versus moderately hypofractionated radiotherapy.

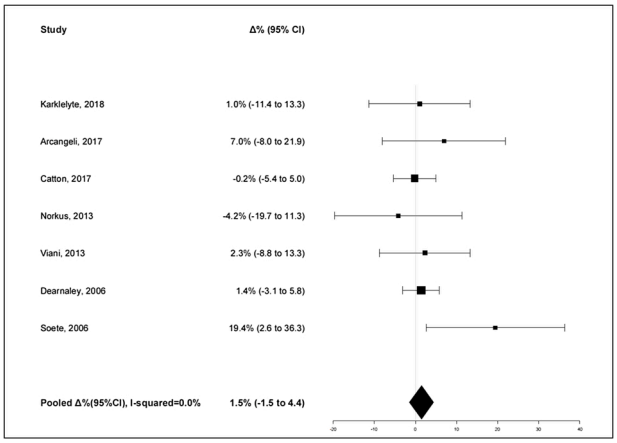

Fig. 3. Pooled analysis of risk of acute genito-urinary (GU) toxicity after conventionally versus moderately hypofractionated radiotherapy.

Indeed, sensitivity analysis showed that when doses ≥ 75 Gy are administered in the conventional cohort, this effect might be reduced. Thus, impact of hypofractionation on acute GI toxicity may be lower when isoeffective doses are compared. Moreover, high heterogeneity in the results ($I^2 = 57$ %) underlines the impact of small studies on overall cohort.

In terms of GU toxicity, small increase in terms of acute GU toxicity could be considered negligible, especially considering the wide

Table 2
Risk of bias assessment performed with Cochrane risk of bias tool.

	Aluwini, 2016	Arcangeli, 2017	Catton, 2017	Dearnaley, 2016	Karklelyte, 2018	Soete, 2006	Viani, 2013	Reviewer comments
SELECTION BIAS Random Sequence Generation	Low	Low	Low	Low	Low	Low	High	
SELECTION BIAS Allocation Concealment	Low	Low	Low	Low	Low	Low	High	
REPORTING BIAS Selective Reporting	Low	Low	Low	Low	Low	High	Low	
PERFORMANCE BIAS Blinding (participants and personnel)	Low	Low	Low	Low	Low	Low	Unclear[a]	[a]*Possible influence of treatment arm on toxicity management*
DETECTION BIAS Blinding (outcome assessment)	Low	Low	Low	Low	Low	High	Low	
ATTRITION BIAS Incomplete Outcome Data	Low	Low	Low	Low	Low	Low	Low	
OTHER BIAS Other Sources of Bias	Low	Low	Low	Low	Low	High[b]	Low	[b]*Follow up was not reported for Soete et al study*

confidence interval, compatible with both harm and benefit yielded by intervention arm. In this case, results appear reliable also looking at low heterogeneity level reported ($I^2 = 0\%$).

It is important to consider also that only two trials (Dearnaley et al., 2016; Karklelyte et al., 2018) included exclusively patients treated with Intensity Modulated RT (IMRT). Given the wide availability of this technique and the benefit of IMRT in this setting (Sharma et al., 2007), 3D conformal RT should not be considered the standard approach to administer dose-escalated prostate RT with curative intent. Another issue to be considered is related to different target volumes definition in the trials included. Whole pelvis prophylactic treatment was not administered in most included trials, but this was considered standard approach in Norkus et al. study, and this could have influenced reported GI toxicity (Norkus et al., 2013). Furthermore, dose prescriptions were heterogeneous; for example, 80 %, 96 % and 100 % of prescribed dose were required to cover prostate and base of seminal vesicles, prostate with 1 cm margins and prostate with 0.5 cm margins within the CHHiP trial, respectively (Dearnaley et al., 2016). In practice, lower coverage on a portion of PTV was allowed in this case. Similar approach may help to decrease dose to rectum and GI toxicity, but some clinician could feel that underdosage to seminal vesicles may negatively influence treatment outcomes, especially when seminal vesicles involvement is detected. On the other hand, PTV received at least 95 % of prescribed dose in the trials by Norkus and (Catton et al. (2017); Norkus et al., 2013), while 95 and 90 % of PTV were covered by the prescription dose in the Viani and Arcangeli et al. trials, respectively (Arcangeli et al., 2017; Viani et al., 2013). A thorough quality assessment of these trials would be necessary to allow a reliable comparison. In terms of risk of bias, high certainty about data from available literature has been detected within the included trials.

5. Conclusions

Overall, majority of trials included in our meta-analysis suggested that moderately hypofractionated RT is equivalent, in terms of GI and GU adverse events, to conventional fractionation. Pooled analysis showed a trend to increased GI toxicity after hypofractionated treatment. However, influence of small trials on this outcome might have been significant. Moreover, differences are reduced when higher iso-effective dose in conventional arm of treatment are compared, suggesting that increased toxicity might be related to dose escalation rather than hypofractionation. Impact of different techniques (e.g 3D conformal vs IMRT) and dose prescriptions on this issue should be explored to define correct standard approach for moderately hypofractionated treatment.

Declaration of Competing Interest

No conflict of interest and financial relationships relevant to the content of this article have to be declared. This paper has not been previously published and has not been submitted for publication.

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