ROJ Radiation Oncology Journal

Review Article

pISSN 2234-1900 · eISSN 2234-3156
Radiat Oncol J 2024;42(3):171-180
https://doi.org/10.3857/roj.2023.01046

Evidence-based clinical recommendations for hypofractionated radiotherapy: exploring efficacy and safety-Part 3. Genitourinary and gynecological cancers

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Received: December 25, 2023
Revised: January 31, 2024
Accepted: February 7, 2024

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Hypofractionated radiotherapy (RT) has become a trend in the modern era, as advances in RT techniques, including intensity-modulated RT and image-guided RT, enable the precise and safe delivery of high-dose radiation. Hypofractionated RT offers convenience and can reduce the financial burden on patients by decreasing the number of fractions. Furthermore, hypofractionated RT is potentially more beneficial for tumors with a low α/β ratio compared with conventional fractionation RT. Therefore, hypofractionated RT has been investigated for various primary cancers and has gained status as a standard treatment recommended in the guidelines. In genitourinary (GU) cancer, especially prostate cancer, the efficacy, and safety of various hypofractionated dose schemes have been evaluated in numerous prospective clinical studies, establishing the standard hypofractionated RT regimen. Hypofractionated RT has also been explored for gynecological (GY) cancer, yielding relevant evidence in recent years. In this review, we aimed to summarize the representative evidence and current trends in clinical studies on hypofractionated RT for GU and GY cancers addressing several key questions. In addition, the objective is to offer suggestions for the available dose regimens for hypofractionated RT by reviewing protocols from previous clinical studies.

Keywords: Radiation dose hypofractionation, Urogenital neoplasm, Genital neoplasm, Female

Introduction

Genitourinary (GU) and gynecological (GY) cancers constitute the majority of primary pelvic malignancies, alongside rectal cancer [1]. Radiotherapy (RT) is widely used for the curative or palliative treatment of GU and GY cancers [2]. The application of RT varies significantly based on the primary cancers and stages and is offered in various combinations and sequences with other modalities, including surgical resection and systemic treatments. While conventional fractionated regimens were traditionally adopted for a considerable period in GU/GY cancers, hypofractionation has increasingly gained acceptance in the past decade [3].

Due to its radiobiological properties, hypofractionated RT is known to be potentially more beneficial for tumors with a low α/β ratio compared with conventionally fractionated RT [4]. Furthermore, hypofractionated RT is acknowledged for providing convenience to patients and increasing economic benefits by reducing the number of fractions [5]. Despite these benefits, there have been concerns regarding the toxicity of hypofractionated RT [6]. However, advancements in RT techniques, including the introduction of intensity-modulated RT (IMRT) and image-guided RT (IGRT), have facilitated the safe delivery of high-dose radiation. This has led to the extension of the use of hypofractionation regimens, and subsequently, substantial evidence on its safety and efficacy has accumulated across various primary malignancies [7].

As a result, hypofractionated RT has gained recognition as one of the standard treatments recommended in the guidelines for various cancers. Based on several landmark clinical trials, hypofractionated RT has become an established standard therapeutic regimen for pelvic cancers, especially GU cancer [2,8,9]. Furthermore, clinical studies demonstrating the efficacy and tolerance of hypofractionated RT for GY cancers have been conducted, with an expected increase in its future use [10,11]. In this context, we have summarized representative evidence and current trends from clinical studies on hypofractionated RT for GU and GY cancers, addressing several key questions (KQs). We have also presented suggestions for dose prescriptions for hypofractionated RT by reviewing protocols from previous clinical studies.

KQ 1. What is the Applicable Hypofractionated RT Regimen in Prostate Cancer?

External beam RT (EBRT) has emerged as the standard definitive treatment for men diagnosed with localized prostate cancer, providing long-term local control comparable to that of radical prostatectomies [12]. Technological advances, including intensity modulation and daily image guidance, have achieved significant progress in EBRT for prostate cancer, allowing higher radiation doses to be delivered to the prostate with a high degree of safety [13].

The linear-quadratic model explains the probability of cell survival after exposure to ionizing radiation [4]. This model describes cell survival curves as a function of radiation dose, showing an initial linear component followed by a steeper quadratic component. The sensitivity of irradiated tissue to fractionation is determined by the relative weighting of these components, represented by the α/β [4]. Prostate cancer is known to have a low α/β compared to most other tumors. Interestingly, the α/β of the adjacent dose-limiting normal structure including the rectum has been estimated to be higher than that of prostate cancer [14]. This suggests that hypofractionation, which involves delivering higher daily doses of EBRT (>200 cGy), may further enhance the therapeutic efficacy for localized prostate cancer [8].

Hypofractionation in EBRT is divided into two categories: "moderate hypofractionation" and "ultra-hypofractionation." Moderate hypofractionation usually refers to EBRT with fraction sizes ranging from 240 to 340 cGy. On the other hand, ultra-hypofractionation, which is referred also as extreme hypofractionation or stereotactic body radiotherapy (SBRT), involves EBRT with a fraction size of 500 cGy or greater. The choice of 500 cGy as the threshold is based on the literature, suggesting that this is the point at which the linear-quadratic model may no longer be valid [15]. The currently accepted definitions of moderate or ultra-hypofractionation were adopted from recent large trials that showed favorable results for hypofractionated EBRT [16-24]. Selected randomized trials comparing hypofractionation with conventionally fractionated EBRT are shown in Fig. 1. These trials revealed that the oncological outcomes of hypofractionated EBRT were comparable to or non-inferior to those of conventionally fractionated EBRT. Furthermore, while there was a concern about the potentially higher risk of toxicity for hypofractionated EBRT, toxicity outcomes, including genitourinary and gastrointestinal toxicities, were also comparable between hypofractionated and conventionally fractionated EBRT in most studies. The detailed toxicity outcomes of the selected trials are summarized in Table 1. Based on these results, various hypofractionated dose regimens are recommended according to the prostate cancer risk groups [2] (Table 2). These clinical trials adopted various dose constraints on the bladder and rectum to spare the adjacent organs, as described in Table 3 [16-24]. These recommendations are based on the previous trials comparing moderate or ultra-hypofractionated versus conventional EBRT. The relevant study regarding the comparison between moderate versus ultra-hypofractionated EBRT is scarce. A phase II trial, however, demonstrated comparable acute toxicity between 70 Gy in 28 fractions and 36.25 Gy in 5 weekly fractions [25]. Further investigation would be necessary for the comparative data between those two types of hypofractionated EBRT.

For adequate hypofractionated EBRT, modern techniques including IMRT and IGRT should be considered, especially when ultra-hypofractionated EBRT is performed [26]. Fiducial markers can be used for precise target localization to enhance the quality of IGRT [27]. The recently introduced hydrogel spacer can be a viable option for reducing the potential risk of rectal bleeding after hypofractionated EBRT [28]. Furthermore, careful patient selection is required for ultra-hypofractionation. The American Society for Radiation Oncology, American Society of Clinical Oncology, and American Urological Association guidelines recommend that patients with a prostate volume of <100 mL, the International Prostate

https://doi.org/10.3857/roj.2023.01046

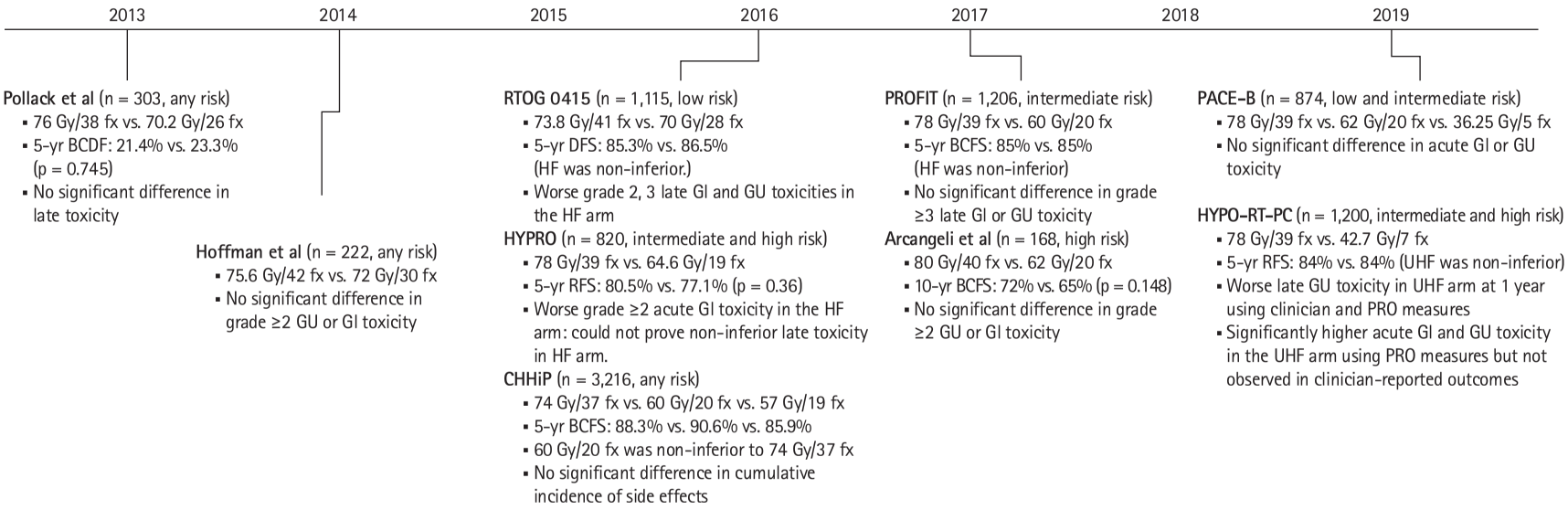

Fig. 1. Timeline of key randomized trials comparing radiotherapy fractionation strategies for prostate cancer. fx, fraction; BCDF, biochemical and/or clinical disease failure; GU, genitourinary; GI, gastrointestinal; DFS, disease-free survival; HF, hypofractionation; RFS, recurrence-free survival; BCFS, biochemical recurrence-free survival; PRO, patient-reported outcome; UHF, ultra-hypofractionation.

Table 1. Summary of toxicity outcomes from selected randomized trials

Study	n	Dose regimen	Acute GU toxicity grade ≥ 2	Acute GI toxicity grade ≥ 2	Late GU toxicity grade ≥ 2	Late GI toxicity grade ≥ 2
Pollack et al. [16]	303	76 Gy/38 fx vs. 70.2 Gy/26 fx	NA	NA	25% vs. 40% (8-year; p = 0.24)	16% vs. 11% (8-year; p = 0.96)
Hoffman et al. [17]	206	75.6 Gy/42 fx vs. 72 Gy/30 fx	NA	NA	16% vs. 16% (5-year; p = 0.98)	5% vs. 10% (5-year; p = 0.10)
RTOG-0415 [18]	1,115	73.8 Gy/41 fx vs. 70 Gy/28 fx	27% vs. 27%	10% vs. 11%	23% vs. 30% (p = 0.06)	14% vs. 22% (p = 0.002)
HYPRO [19]	820	78 Gy/39 fx vs. 64.6 Gy/19 fx	58% vs. 61%	31% vs. 42%	39% vs. 41% (3-year)	18% vs. 22% (3-year)
CHHip [20]	3,216	74 Gy/37 fx vs. 60 Gy/20 fx vs. 57 Gy/19 fx	46% vs. 49% vs. 46% (p = 0.90)	25% vs. 38% vs. 38% (p < 0.0001)	9% vs. 12% vs. 7% (5-year; p = 0.07)	14% vs. 12% vs. 11% (5-year)
PROFIT [21]	608	78 Gy/39 fx vs. 60 Gy/20 fx	27% vs. 27%	10% vs. 16% (p = 0.003)	19% vs. 20%	11% vs. 7% (p = 0.006)
Arcangeli et al. [22]	168	80 Gy/40 fx vs. 62 Gy/20 fx	40% vs. 45% (p = 0.45)	21% vs. 35% (p = 0.07)	21% vs. 14% (p = 0.68)	15% vs. 13% (p = 0.57)
HYPO-RT-PC [24]	1,200	78 Gy/39 fx vs. 42.7 Gy/7 fx	22.8% vs. 27.6% (p = 0.11)	5.3% vs. 9.4% (p = 0.23)	5% vs. 5% (5-year)	4% vs. 1% (5-year)
PACE-B [23]	874	62 or 78 Gy/20 or 39 fx vs. 36.25 Gy/5 fx	NA	NA	2% vs. 3% (2-year; p = 0.39)	3% vs. 2% (2-year; p = 0.32)

fx, fraction; GU, genitourinary; GI, gastrointestinal; NA, not applicable.

Symptom Score of < 20, and non-high-risk disease are considered suitable candidates for ultra-hypofractionated EBRT [8].

KQ 2. What is the Applicable Hypofractionated RT Regimen in Bladder Cancer?

Bladder cancer is the 10th most common cancer worldwide and approximately 25% of patients are diagnosed with muscle-invasive bladder cancer (MIBC) [29]. Although neoadjuvant chemotherapy followed by radical cystectomy remains the primary curative treatment for MIBC, bladder preservation with concurrent chemoradiotherapy (CCRT) is also a recommended option [30]. Generally, patients with MIBC who achieve complete transurethral resection, have small solitary tumors with limited carcinoma in situ, show no hydronephrosis, and maintain good baseline bladder function are considered suitable candidates for bladder preservation [31]. According to these conditions, only 6%–19% of the patients with MIBC are considered ideal for bladder preservation [31]. Bladder preservation with CCRT for MIBC has been investigated over the past 20 years. Previous studies have shown complete response rates of 64%–93%, 5-year bladder preservation rates of 42%–61%, and 5-year overall survival rates of 48%–74% [32]. However, the dose schemes were based on conventional fractionation and were heterogeneous among the studies.

The efficacy of CCRT with hypofractionation was investigated in a pooled meta-analysis of the BC2001 and BCON trials [33,34]. Both trials were randomized controlled trials comparing RT alone and CCRT (BC2001) or RT with carbogen and nicotinamide as hypoxic sensitizers for bladder preservation therapy in patients with

Table 2. Recommended hypofractionation regimens according to the risk group

NCCN risk group	Recommended regimen
Very low and low	MH[a], UHF[c]
Favorable intermediate	MH[a], UHF[c]
Unfavorable intermediate	MH[a], UHF[c]
High and very high	MH[a], UHF[c]
Regional N1	MH[a]
Low volume M1[e]	MH[b], UHF[d]

NCCN, National Comprehensive Cancer Network; MH, moderate hypofractionation; UHF, ultra-hypofractionation.
[a]3 Gy × 20 fx, 2.7 Gy × 26 fx, 2.5 Gy × 28 fx; [b]2.75 Gy × 20 fx; [c]9.5 Gy × 4 fx, 7.25-8 Gy × 5 fx, 6.1 Gy × 7 fx; [d]6 Gy × 6 fx.
[e]High-volume disease is differentiated from low-volume disease by visceral metastases and/or four or more bone metastases with at least one metastasis beyond the pelvis and/or vertebral column.

Table 3. Dose constraints for hypofractionation in selected trials for bladder and rectum

Study	Dose regimen of hypofractionation	Bladder	Rectum	Femoral heads	Penile bulb
Pollack et al. [16]	70.2 Gy/26 fx	V_{50Gy} < 25% V_{31Gy} < 50%	V_{50Gy} < 17% V_{31Gy} < 35%	NA	NA
Hoffman et al. [17]	72 Gy/30 fx	V_{65Gy} < 20%	V_{65Gy} < 20%	V_{45Gy} < 10%	NA
RTOG-0415 [18]	70 Gy/28 fx	V_{79Gy} < 15% V_{74Gy} < 25% V_{69Gy} < 35% V_{64Gy} < 50%	V_{74Gy} < 15% V_{69Gy} < 25% V_{64Gy} < 30% V_{59Gy} < 50%	NA	D_{mean} ≤ 51 Gy
CHHiP [20]	60 Gy/20 fx	V_{60Gy} ≤ 5% $V_{48.6Gy}$ ≤ 25% $V_{40.8Gy}$ ≤ 50%	V_{60Gy} ≤ 3% V_{57Gy} ≤ 15% $V_{52.8Gy}$ ≤ 30% $V_{48.6Gy}$ ≤ 50% $V_{40.8Gy}$ ≤ 60%	$V_{40.8Gy}$ < 50%	$V_{48.6Gy}$ ≤ 10% $V_{40.8Gy}$ ≤ 50%
PROFIT [21]	60 Gy/20 fx	V_{37Gy} < 50% V_{46Gy} < 70%	V_{37Gy} < 50% V_{46Gy} < 70%	NA	NA
Arcangeli et al. [22]	62 Gy/20 fx	V_{54Gy} ≤ 50% V_{39Gy} ≤ 70%	D_{max} ≤ 62 Gy V_{54Gy} < 30% V_{39Gy} < 50%	D_{max} ≤ 42 Gy	NA
HYPO-RT-PC [24]	42.7 Gy/7 fx	NA	$V_{38.4Gy}$ ≤ 15% V_{32Gy} ≤ 35% V_{28Gy} ≤ 45%	D_{max} ≤ 29.9 Gy	NA
PACE-B [23]	36.25 Gy/5 fx	$V_{18.1Gy}$ < 40% V_{37Gy} < 10 mL	$V_{18.1Gy}$ < 50% V_{29Gy} < 20% V_{36Gy} < 1 mL	$V_{14.5Gy}$ < 5%	$V_{29.5Gy}$ < 50%

fx, fraction; NA, not applicable; D_{mean}, mean dose; D_{max}, maximum dose; V_{dose}, the irradiated volume exceeding a defined dose.

https://doi.org/10.3857/roj.2023.01046

MIBC. Each trial allowed both 55 Gy in 20 fractions and 64 Gy in 32 fractions as the RT regimens. The meta-analysis demonstrated the superiority of hypofractionation (55 Gy in 20 fractions) in invasive locoregional control with an adjusted hazard ratio (HR) of 0.71 (95% confidence interval [CI], 0.52–0.96) and non-inferiority in overall survival with HR of 0.87 (95% CI, 0.72–1.06) along with late toxicities in bladder and rectum with adjusted risk difference of -3.37 (95% CI, -11.85–5.10) [9]. Based on the results of this meta-analysis, hypofractionation at 55 Gy in 20 fractions is recommended as a reasonable alternative to conventional fractionation.

However, the optimal target volume has not yet been established. In both trials, all patients received whole-bladder RT without elective pelvic nodal irradiation (EPNI) generating a clinical target volume (CTV) including the whole bladder with any extravesical extension of tumor [33,34]. In the BC2001 trial, another randomization, other than RT alone versus CCRT, was conducted based on the target volumes: standard whole-bladder RT versus reduced high-dose volume RT (RHDVRT) [35]. In the standard whole-bladder RT arm, CTV was defined as the whole bladder with any extravesical extension as usual, and a 1.5-cm margin was added to the CTV to create the planning target volume (PTV). In contrast, in RHDVRT arm, the PTV1 was defined as a 1.5-cm expansion from the whole bladder while PTV2 was defined as 1.5 cm expansion from the gross tumor in the bladder. PTV2 was planned to receive 100% of the prescribed 55 Gy in 20 fractions and PTV1 to receive 80% of the prescribed dose. The study failed to show a statistically significant reduction in the late side effects of RHDVRT, and concluded the non-inferiority of locoregional control. However, the overall low rates of toxicity and relapse of invasive bladder cancer imply the feasibility of both target volumes. In addition to the target volume for the whole bladder, the necessity of EPNI in hypofractionated RT for MIBC remains unclear [36]. Only one randomized clinical trial has compared whole-bladder RT versus whole-bladder RT and EPNI, showing no benefit of additional EPNI [37]. However, a quarter of patients with clinically node-negative MIBC demonstrate occult pelvic node involvement at radical cystectomy plus pelvic lymph node dissection, so the omission of EPNI should be carefully decided [38]. The National Comprehensive Cancer Network (NCCN) guideline for bladder cancer described that EPNI is optional and should consider patients' comorbidities and the risk of toxicity to adjacent organs [39].

Although EPNI is optional, EPNI is still commonly performed in the United States [40]. Therefore, for patients with MIBC and a high risk of pelvic node recurrence, hypofractionated RT with EPNI should be considered. For hypofractionated RT with EPNI, a reasonable regimen can be 40–44 Gy in 20 fractions of EPNI with a simultaneous boost of 55 Gy in 20 fractions to the whole bladder [36]. However, further studies are required to confirm this hypothesis. Because hypofractionation can increase the risk of toxicity, appropriate dose constraints for adjacent organs at risk are required. The suggested dose constraints for hypofractionated RT for MIBC are presented in Table 4 [41].

Ultra-hypofractionated RT has also been suggested for bladder cancers. In the HYBRID trial, a phase II randomized trial, patients with clinically node negative MIBC who were unsuitable for radical cystectomy were treated with 36 Gy in 6 weekly fractions. The trial involved randomization to either standard planning or plan-of-the-day adaptive planning using cone beam computed tomography [42]. The median age of the patients was 85 years. In this study, the 1-year local control (LC) rate was 71.7% and the 1-year invasive local recurrence-free rate was 85.5%. Adaptive planning showed low rates of non-GU and GU toxicity of grade ≥3 compared with that of standard planning. Despite some limitations including an insufficient follow-up duration of a median of 38.8 months, a small sample size, and a biased age distribution, this study implied that adaptive ultra-hypofractionated RT is feasible for elderly patients. Further clinical studies are necessary to generalize the feasibility of this regimen for patients with MIBC.

KQ 3. What are the Indications, Efficacy, and Toxicity of SBRT Boost in Cervical Cancer Patients instead of Brachytherapy Boost?

The standard treatment for locally advanced cervical cancer includes EBRT and concurrent chemotherapy followed by a brachytherapy boost. A brachytherapy boost is essential as it limits the irradiation of adjacent normal organs while increasing the dose to the primary tumor, leading to a higher survival rate [43]. With the implementation of magnetic resonance imaging-based brachytherapy, the 5-year LC reached 92%, significantly superior to the results of two-dimensional brachytherapy [44]. The 5-year overall survival (OS) exceeded 76% in stages IB–IIIA and ranged from 52% to 64% in stages IIIB–IVB. The overall 5-year cumulative incidence of grade ≥3 morbidity was 18.4%. However, when analyzed per organ the

Table 4. Suggested dose constraints for hypofractionated radiotherapy for bladder cancer

Structure	Dose constraint
Rectum	D_{mean} < 40 Gy
	V_{50Gy} < 50%
Small bowel	V_{50Gy} < 98 mL
Femoral head	V_{50Gy} < 50%

D_{mean}, mean dose; V_{dose}, the irradiated volume exceeding a defined dose.

incidence ranged from 3.2% to 8.5%. Most grade ≥3 toxicities occurred in patients with stage III–IVA disease.

Despite its favorable LC, the use of brachytherapy has decreased in South Korea due to low medical reimbursement, high expenses for source replacement, and a shortage of human power [45]. Additionally, driven by the advances in EBRT techniques, there has been a global attempt to replace brachytherapy with an EBRT boost, despite several guidelines emphasizing the value of brachytherapy [46]. SBRT regimens have often been applied to reduce the discrepancy between brachytherapy and EBRT boosts.

No prospective randomized controlled studies have compared brachytherapy and SBRT boosts for cervical cancer. A few studies have evaluated the efficacy and toxicity of SBRT boost (Table 5). All studies enrolled patients who were either unsuitable for brachytherapy (e.g., inability to identify the cervical os, obstruction of cervical os by the tumor mass, anatomical variations such as uterus bicollis or bicornis, or medical comorbidities) or refused brachytherapy [18,47-53]. Most studies were retrospective and had a small number of patients, mostly below 30.

Three studies reported OS or LC of 100% and had no grade ≥3 toxicities. However, they had only 6 and 11 patients and less than 2 years of follow-up [47-49]. Studies with over 2 years of follow-up reported a 3-year LC of 78%–92%, and OS of 41%–60% which were lower than those of brachytherapy. Only one phase II study reported a 2-year cumulative incidence of toxicity grade ≥3 of 26.7% [53]. Another retrospective study that enrolled 56% of the patients with stage III or more also reported a toxicity of grade ≥3 of 23.8% [54]. The largest study with 31 patients reported only one grade 3 toxicity, but a significant proportion of the study's participants, specifically 22 patients (71%) had stage II disease or less. Therefore, brachytherapy remains a clear standard of care, whereas an SBRT boost may be applicable to carefully selected patients who are not candidates for brachytherapy or who refuse it.

Various techniques and doses for SBRT boost are considered. The doses varied from 23.3 Gy to 40 Gy, converting to a biological equivalent dose in 2 Gy fractions (EQD2) with α/β ratio of 10. Currently, it is difficult to recommend a specific dose regimen for SBRT boost. However, dose escalation over EQD2 80 Gy might be related to increased toxicity, considering the results of Morgenthaler et al. [52]. Extrapolating the fact that the incidence of grade ≥3 morbidity was higher in stage III–IVA [44] in a brachytherapy setting owing to its large extent of disease, modest SBRT doses should be applied to the patients with stage III or more.

Table 5. Studies[a] of SBRT as a boost in patients with cervical cancer

Author (setting)	n	Stage	Patients' inclusion	Median follow-up (range)	EBRT	SBRT boost technique & dose	Treatment outcome		Grade ≥3 toxicity
							OS	LC	
Haas et al. [47] (R)	6	IIB (4), IV (2)	Not suitable for BT or refuse BT	14 mo (1–28)	45 Gy/25 fx	CK & 20 Gy/5 fx or 19.5 Gy/3 fx	100%	100% in 5 pts with a minimum of 1 year	None
Marnitz et al. [48] (R)	11	IIB (9), IIIB (2)	Not suitable for BT	6 mo	50.4 Gy/28 fx	CK & 30 Gy/5 fx	100%	100%	None
Ito et al. [49] (P, Phase I)	6	IIIA (2), IIIC (4)	Not suitable for BT	17 mo (8–32)	45 Gy/25 fx	LINAC & 19.5–22.5 Gy/3 fx	NA	100%	None
Facondo et al. [50] (R)	9	II (5), III (2), IVA (2)	Not suitable for BT	16 mo (6–58)	50.4 Gy/28 fx	LINAC & 12–25 Gy/2–5 fx	2-year 70%	1 recurrence	Acute: None
Hsieh et al. [51] (R)	9	IIB (4), IIIB (3), IVA (2)	Not suitable for BT	36 mo	50–50.4 Gy/25–28 fx	Tomotherapy & 16–27 Gy/5–9 fx	47%	78%	Acute: 2 pts
Morgenthaler et al. [52] (R)	31	I (2), II (20), III (4), IVA (5)	Not suitable for BT or refuse BT	40 mo (5–84)	50.4 Gy/28 fx	CK & 25–30 Gy/5 fx	3-year 60%	3-year 92%	Acute: 1 pt
Lee et al. [54] (R)	25	I–II (11), III (9), IV (5)	Not suitable for BT	34 mo (4–79)	44–50.4 Gy/25–28 fx	LINAC & 20–33 Gy/4–6 fx	3-year 41%	3-year 81%	5/21 pts (23.8%)
Albuquerque et al. [53] (P, Phase II)	12	I–II (7), III (6), IV (2)	Not suitable for BT or refuse BT	19 mo	45 Gy/25 fx	LINAC & 28 Gy/4 fx	2-year 53%	2-year 70%	2-year 26.7%

BT, brachytherapy; EBRT, external beam radiotherapy; SBRT, stereotactic body radiotherapy; CK, CyberKnife; OS, overall survival; LC, local control; pts, patient(s); LINAC, linear accelerator; pt, patient; mo, month; P, prospective; R, retrospective; fx, fraction; NA, not available.

[a]Search strategy and selection criteria: PubMed was searched for English language publications, using search queries including synonyms of "uterine cervical cancer," "SBRT," and "boost" as follows: (Cervix OR Cervical) AND (Stereotactic OR Ablative OR Robotic OR CyberKnife OR Radiosurgery) AND (Boost OR Brachytherapy). Randomized controlled trials (including subgroup analyses), meta-analyses, reviews, retrospective studies, and cohort studies were included, but not abstracts or dosimetric planning studies, from January 2005 to July 2023. Meeting abstracts from international conferences were also considered. A consensus was reached through group discussion.

https://doi.org/10.3857/roj.2023.01046

KQ 4. What are the Indications, Efficacy, and Toxicity of Hypofractionated Postoperative Radiotherapy in Gynecological Cancer Patients?

Postoperative radiotherapy (PORT) plays an important role in the treatment of gynecological cancers, particularly cervical and endometrial cancers. The standard CTV for PORT includes the pelvic lymph nodes, postoperative beds, and upper vagina [55]. IMRT has been shown to reduce gastrointestinal and GU toxicities compared with that of conventional radiation techniques [56]. However, the dose regimens for PORT in gynecological cancers still typically span 5 to 6 weeks, constituting a prolonged schedule that can burden patients in terms of quality of life and costs. Owing to the coronavirus disease 2019 pandemic, attempts have been made to adopt a hypofractionated schedule.

Although hypofractionation is well established in rectal and prostate cancers, limited research has been conducted on hypofractionation in gynecological cancers. There has been only one phase I/II prospective trial [57], one retrospective study [58], and one case report [59] (Table 6). The phase I/II study enrolled 61 patients with endometrial cancer and evaluated the safety of a dose of 30 Gy in 5 fractions every other day or once weekly [57]. With only one case of grade 3 diarrhea, this stereotactic hypofractionated regimen was well tolerated at a median follow-up of 9 months. Another retrospective study conducted from 2004 to 2007 involved patients who received three-dimensional conformal RT [58]. However, there was no grade 2 toxicity, and the incidence of grade 2 toxicity was minimal, possibly attributed to the cytoprotective effect of amifostine.

Ongoing phase II studies in Korea include the postoperative hypofractionated intensity-modulated (POHIM)-RT and POHIM-CCRT trials. These studies aim to evaluate the acute toxicities of postoperative hypofractionated IMRT (40 Gy in 16 fractions) in patients with cervical cancer who underwent radical hysterectomy. Although the final results are pending, the group reported sigmoid colon perforation 1 month after PORT [59]. It is difficult to attribute this event to hypofractionation, as other studies have demonstrated acceptable toxicity profiles.

There have been some reports on carbon ion radiotherapy as definitive radiotherapy for cervical cancer, mostly using hypofractionation regimens, such as 39 GyE in 13 fractions [60] or 36 GyE in 12 fractions [61]. These regimens for whole pelvic irradiation demonstrated grade ≥3 toxicities in the range of 1.7%–6.5%, and hence could be followed by further irradiation up to around 70 Gy, making hypofractionated PORT a safe and convenient option for patients with gynecological cancers. However, there is currently limited oncological outcome data and longer follow-up data on safety. Hypofractionated PORT should be considered in clinical trials with sufficient consultation with patients, particularly for selected patients with poor performance who cannot afford the 5- to 6-week conventional treatments.

Conclusion

For genitourinary cancer, a variety of hypofractionation regimens have been studied and utilized in real-world practice. Further investigation is necessary to explore the feasibility of ultra-hypofractionated RT and determine the best hypofractionation regimen. In contrast, the adoption of hypofractionation seems slow in gynecologic cancers, where brachytherapy remains the clear standard of

Table 6. Studies[a] of hypofractionated postoperative radiotherapy in gynecological cancer patients

Author (setting)	n	Primary	Combined treatments	Median follow-up	Radiation technique & dose	Treatment outcome		Toxicity
						OS	LC	
Leung et al. [55] (P, Phase I/II)	61	EM	Sequential CTx (16), vaginal BT (9)	9 mo (IQR, 3–15)	VMAT & 30 Gy/5 fx (EOD or weekly)	NA	NA	GI: G2 (13%), G3 (1.6%) GU: G2 (3%)
Koukourakis et al. [56] (R)	25	EM (22), Cx (3)	Cytoprotetion (amifostine)	31 mo	3D-CRT & 37.8 Gy/14 fx followed by boost 12 Gy/3–4 fx	100%	100%	Acute: G2 (8%) Late: G2 (4%) No G3
Kim et al. [57] (C)	1	Cx	None	1 mo	IMRT & 40 Gy/16 fx	NA	NA	Sigmoid perforation at 1 mo

OS, overall survival; LC, local control; EM, endometrium; Cx, cervix; CTx, chemotherapy; mo, month; BT, brachytherapy; VMAT, volumetric-modulated arc therapy; EOD, every other day; G, grade; 3D-CRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; GI, gastrointestinal; GU, genitourinary; P, prospective; R, retrospective; C, case report; IQR, interquartile range; fx, fraction; NA, not available.

[a]Search strategy and selection criteria: PubMed was searched for English language publications, using search queries including synonyms of "uterine cervical cancer," "endometrial cancer," "postoperative radiotherapy," and "hypofractionation" as follows: (Uterus OR Uterine OR Endometrial) AND (Cervix OR Cervical) AND (Hypofractionated OR Hypofractionation) AND (Radiation OR Chemoradiation OR Radiotherapy OR Chemoradiotherapy) AND (Postoperative OR Adjuvant). Randomized controlled trials (RCTs) (including subgroup analyses), meta-analyses, reviews, retrospective studies, and cohort studies were included, but not abstracts or dosimetric planning studies, from January 2005 to July 2023. Meeting abstracts from international conferences were also considered. A consensus was reached through group discussion.

care for boost treatment. The results of the POHIM trials should be awaited.

Statement of Ethics

Because this study did not involve any human subjects, Institutional Review Board approval and informed consent were not required.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Funding

None.

Author Contributions

Conceptualization, GSY, YJK; Investigation and methodology, GSY, YJK; Project administration, YSK; Resources & Writing of the original draft, GSY, YJK; Supervision & Writing of the review and editing, YSK, SYS, JHS, BHK, KYK, KSK, HKB; Data curation, YSK, SYS, JHS, BHK, KYK, KSK, HKB. All the authors have proofread the final version.

Data Availability Statement

The data that supports the findings of this study are available upon request from the corresponding author.

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 https://doi.org/10.3857/roj.2023.01046