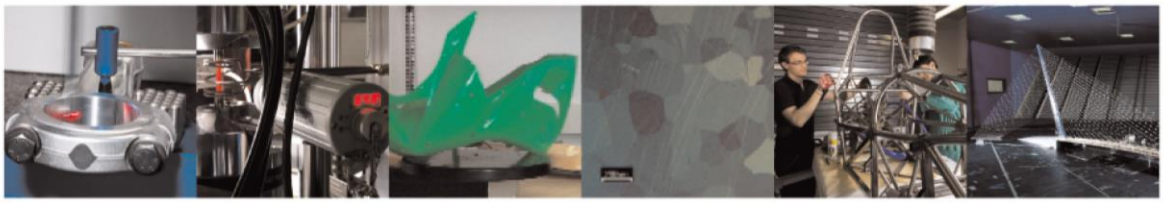

Salvage stereotactic body radiotherapy (SBRT) for intraprostatic relapse after prostate cancer radiotherapy: An ESTRO ACROP Delphi consensus

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Salvage stereotactic body radiotherapy (SBRT) for intraprostatic relapse after prostate cancer radiotherapy: an ESTRO ACROP Delphi Consensus

Running title: *ESTRO ACROP Consensus on prostate salvage SBRT*

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List of abbreviations

ACROP	Advisory Committee on Radiation Oncology Practice
AIRO	Italian Association of Radiotherapy and Clinical Oncology
ADT	Androgen deprivation therapy
ASTRO	American Society for Therapeutic Radiology and Oncology
B~~R~~T	Brachytherapy
CTV	Clinical target volume
EAU	European Association of Urology
EBRT	External beam radiotherapy
ECOG	Eastern Cooperative Oncology Group
ESTRO	European SocieTy for Radiotherapy and Oncology
IC	Internal Committee

IPSS	International Prostate Symptom Score
G	Grade
GEC	Groupe Européen de Curiethérapie
GTV	Gross tumour volume
HDR-BT	High dose-rate BT
Kendall's W	Kendall's coefficient of concordance
MADM	Mean absolute deviation from the median
mp-MRI	Multiparametric MRI
MRI	Magnetic resonance imaging
NRG	National Surgical Adjuvant Breast and Bowel Project (NSABP) Radiation Therapy Oncology Group (RTOG) Gynecologic Oncology Group (GOG)
OAR	Organ at risk
PCa	Prostate cancer
PET	Positron emission tomography
ProtecT	Prostate Testing for Cancer and Treatment
PSA	Prostate-specific antigen
PSMA	Prostate-specific membrane antigen
QoL	Quality of life
RC	Reviewing Committee
RP	Radical prostatectomy
RT	Radiotherapy
SBRT	Stereotactic body radiotherapy
US	Ultrasound
WC	Writing Committee

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Abstract

Background and purpose Between 30% and 47% of patients treated with definitive radiotherapy (RT) for prostate cancer are at risk of intraprostatic recurrence during follow-up. Re-irradiation with stereotactic body RT (SBRT) is emerging as a feasible and safe therapeutic option. However, no consensus or guidelines exist on this topic. The purpose of this ESTRO ACROP project is to investigate expert opinion on salvage SBRT for intraprostatic relapse after RT.

Materials and Methods A 40-item questionnaire on salvage SBRT was prepared by an internal committee and reviewed by a panel of leading radiation oncologists plus a urologist expert in prostate cancer. Following the procedure of a Delphi consensus, 3 rounds of questionnaires were sent to selected experts on prostate re-irradiation.

Results Among the 33 contacted experts, 18 (54.5%) agreed to participate. At the end of the final round, participants were able to find consensus on 14 out of 40 questions (35% overall) and major agreement on 13 questions (32.5% overall). Specifically, the consensus was reached regarding some selection criteria (no age limit, ECOG 0-1, satisfactory urinary flow), diagnostic procedures (exclusion of metastatic disease, SBRT target defined on the MRI) and therapeutic approach (no need for concomitant ADT, consideration of the first RT dose, validity of Phoenix criteria for salvage SBRT failure).

Conclusion While awaiting the results of ongoing studies, our ESTRO ACROP Delphi consensus may serve as a practical guidance for salvage SBRT. Future research should address the existing disagreements on this promising approach.

Keywords: Recurrent prostate cancer, salvage radiotherapy, stereotactic body radiotherapy, Delphi consensus

1. Introduction

Prostate cancer (PCa) is the second most frequent cancer diagnosis in men and the fifth leading cause of death worldwide [1]. Nowadays, the increased prostate specific antigen (PSA) surveillance and new imaging tools such as multiparametric magnetic resonance imaging (mp-MRI) have significantly improved the detection of clinically relevant disease. Therefore, PCa is nowadays diagnosed at a relatively younger age, and the patients have consequently a longer lifetime and a higher risk of developing recurrence after the first treatment of the primary tumour.

Options at the first diagnosis are radiotherapy (RT), radical prostatectomy (RP) or active surveillance. In low-risk PCa, active surveillance is now the recommended approach, while in intermediate- and high-risk patients, local therapies such as RP or RT are preferred [2]. The ProtecT (Prostate Testing for Cancer and Treatment) trial [3] which reported 10-year follow up of the three treatment groups, demonstrated that RT and surgery were equally associated with a lower rate of disease progression when compared to active monitoring.

Biochemical and clinical recurrent PCa occurs in a percentage of patients varying from 30% to 47% after primary treatment with RT [4]. The current challenge in managing PCa recurrence is to define a tailored treatment option that prevents the onset of metastatic disease or symptomatic local progression and at the same time has the least negative impact on quality of life (QoL).

The most appropriate therapeutic approach for this clinical scenario remains a matter of debate [5–7]. Androgen deprivation therapy (ADT) and salvage RP [8] are viable options, even though they may be burdened by several related complications [9]. As a matter of fact, salvage RP has been associated with significant side effects such as urinary incontinence and may be contraindicated in elderly patients or in the presence of comorbidities [10]. Analogously, ADT, which is the standard of care according to international guidelines [11], represents a serious burden in terms of acute and late effects that seriously affect QoL [9,12].

On the other hand, local approaches such as brachytherapy (BRT) and stereotactic body radiotherapy (SBRT) have been gaining interest, as they are less invasive and able to control the disease without excessive side effects [13,14]. In particular, a recent meta-analysis comparing different local salvage approaches favoured non-surgical modalities, in particular re-irradiation with high dose-rate (HDR) BT, as it was associated with lower severe genitourinary and gastrointestinal toxicities, without compromising the oncological outcome[15]. In a similar manner, a systematic review endorsed by the Italian Association of Radiotherapy and Clinical Oncology (AIRO) reported how re-irradiation of local failures from PCa demonstrated a safe toxicity profile maintaining promising overall mortality

and biochemical control rates[16]. However, apart from the recently published results of the prospective trial on transperineal ultrasound-guided BRT for locally recurrent PCa after EBRT (NRG/RTOG 0526) [17], no further definitive data are currently available concerning the use of BRT as a salvage option for recurrent PCa. A recent Uro-GEC-ESTRO (Groupe Européen de Curiethérapie – European Society for Radiotherapy and Oncology) consensus study by Kaljouw et al. [12], investigating expert opinion on salvage BRT, showed that there are still many areas of disagreement. SBRT, which enables the delivery a high dose of radiation to a very restricted area, has been emerging as a safe alternative salvage treatment option, with both good disease-free survival and reasonable toxicity levels [4,18–24].

A recently published work [25] reported the results of a survey endorsed by the Italian Association of Radiotherapy and Clinical Oncology (AIRO) investigating the role of SBRT for local PCa relapse after RT. The study highlighted the interest towards salvage SBRT in Italy and showed that, even though there are some aspects of re-irradiation the Italian radiation oncologists agree on, there are many others which still represent a matter of debate. Apart from this study, to the best of our knowledge, no international guidelines or clinical indications exist on the use of salvage SBRT.

To fill this gap, the present study, endorsed by the European Society for Radiotherapy and Oncology Advisory Committee on Radiation Oncology Practice (ESTRO ACROP), investigated expert opinion on PCa recurrence re-irradiation with SBRT. To perform this task, a Delphi technique was applied. The Delphi technique was developed in the '50s and has been used in various fields of study proving itself as a well-suited method for consensus-building [26]. The method consists of a series of questionnaires administered in an iterated manner to a pool of experts to collect opinion on the topic of interest. Through the adoption of this technique, the final aim of the study is to seek consensus and provide useful information concerning the use for salvage SBRT in PCa recurrence.

2. Materials and Methods

2.1 Questionnaire drafting and study workflow

The questionnaire was modelled referring to the above-mentioned work on salvage BRT for PCa [12] and on a literature search on the topic carried out by the members of the so-called *Internal Committee* between March to June 2019. A *Reviewing Committee*, composed of a panel of leading radiation oncologists plus a urologist nominated by the European Association of Urology (EAU) society expert in prostate cancer, edited the questionnaire and approved a final version. The definitive list of questions was implemented online via Google Forms and sent to the experts on prostate re-irradiation,

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namely the *Writing Committee* (*Table S1*). Such experts were selected from among authors of eminent scientific papers on this topic [4,7,31–37,18,19,21,22,27–30].

The first version of the questionnaire included 40 questions, dealing with controversial issues related to salvage SBRT and was divided in three sections:

(1) patient selection criteria for prostate salvage SBRT (19 questions);

(2) imaging and biopsy-based tests for diagnosis of recurrence (7 questions);

(3) dosimetric issues on both clinical target volume (CTV) and organs at risk (OARs) (14 questions).

Thirty-nine questions were multiple-choice, 37 with mutually exclusive choices and two had the possibility of more than one answer, ~~1~~ one question was open-ended. In the time frame between July 22nd and December 16th, 2019, the search for consensus was pursued by submitting the questionnaire in three rounds to the experts' pool, in accordance with the Delphi scheme. After each round was concluded, the participants received a fully anonymised summary of their and others' responses ~~fully anonymised~~. This feature is an important characteristic of any Delphi study, as it reduces the possible influence of some responders on the others. The feedback is supposed to drive the panellists towards the consensus. Based on the respondents' answers and possible comments, some questions were slightly modified in the second and third rounds. Responses with more than 80% agreement in one round were removed from the next one as consensus was considered reached. The study workflow is illustrated in detail in *Figure 1*.

An additional round of new questions was submitted to retrieve additional information about institution characteristics and technical equipment for each respondent. Survey participation was voluntary with no financial incentives for responders. This survey study did not require ethical approval as it was non-interventional, and no patients or patient data were involved. The study manuscript was reviewed by external experts indicated by the ESTRO ACROP Committee and its final version was approved by all authors.

2.2 Statistical analysis

For each item a rating scale was defined assigning value 1 to the question recorded the highest response rate in the third round. Items with more than one valid response were divided in sub items, one for each possible answer, counting how many times each modality was chosen at least one time. Kendall's coefficient of concordance (Kendall's W) was used to evaluate consensus among participants for each section of the questionnaire during the three rounds [38]. Kendall's W is a non-

parametric statistic test used for assessing agreement among raters and ranges from 0 (no agreement) to 1 (complete agreement). Kendall's W ≥ 0.7 was considered as strong agreement, Kendall's W between 0.3 and 0.7 as moderate agreement and Kendall's W ≤ 0.3 as a weak agreement. The extent of agreement for each item in the questionnaire was indicated by mean absolute deviation from the median (MADM), which is a measure of the average of the participants' rating from the group's median rating [39].

3. Results

Among the 33 contacted authors of studies on prostate salvage SBRT, 18 (54.5%) agreed to participate in the study. The rate of return of the survey was comparable with the study model [12] and all responders completed all rounds (*Table S2*) (contrary to the Uro-GEC-ESTRO study where one responder did not complete the rounds). Half of the responders currently work in a public hospital and half in private facilities. Only 2 experts responded from centres outside Europe, specifically from the United States. Most experts (12/18, 67%) work in large RT facilities, treating more than 2,000 patients per year (*Table 1*).

At the end of the 3 rounds, consensus was reached in 14/40 questions (35% overall), with half of the consensus built in the first round (7/14). In the second round, consensus increased and was achieved on 4 additional questions. Overall, in the first section of the questionnaire consensus was reached in 6 out of 19 questions, in the second and in the third section consensus was reached in 3 out of 7 and 5 out of 14 questions respectively (*Table S3*). *Figure 2* shows how agreement evolved from the first to the third round. The main findings of the survey are summarized in the *Table 2.*

3.1 Section 1 - Patients' selection criteria for prostate salvage SBRT

Consensus in first section of the questionnaire was achieved in the 32% of the questions, with a Kendall's W coefficient of 0.17, indicating on average a weak agreement. More than 80% of responders have the opinion that age should not be a selection criterion for salvage SBRT and virtually all responders (94%) agreed that the recommended Eastern Cooperative Oncology Group (ECOG) performance status grade should fall between 0 and 1. Regarding hormone therapy, the experts agreed that previous ADT should not be considered a contraindication for salvage SBRT. At the second round, the experts' pool reached consensus that the gross tumour volume (GTV) plus an adaptive margin should be considered as CTV. Opinions were divided whether late toxicity of first RT should

be taken into account. 56% would not deliver salvage SBRT in patients who had experienced grade (G)2+ toxicity, while the remainder raised the threshold to G3+.

3.2 Section 2 – Imaging and biopsy-based test for diagnosis of recurrence

In the second section, consensus was reached in 43% of the questions, resulting in a Kendall's W coefficient of 0.34, indicating on average a moderate agreement on the topic. Agreement was achieved on the evaluation of metastatic disease, considered as important by all the experts, as well as on the imaging methodology to detect eventual metastases, with choline positron emission tomography (PET indicated by 89% of responders. On the other hand, only 28% voted for prostate-specific membrane antigen (PSMA)-PET. Regarding prostate biopsy, only 22% of participants agreed that it is always needed for diagnosis of recurrence.

3.3 Section 3 - Dosimetric issues on CTV and OARs

Consensus was reached in 36% of the questions regarding dosimetric indications. The Kendall's W coefficient of this section (0.12) indicates on average a very weak agreement. Participants agreed that a) ADT should not be delivered concomitantly with RT; b) the RTOG-ASTRO Phoenix definition [40] of biochemical relapse is valid in the follow-up of retreated patients; c) the dose of primary treatment should be taken into account when deciding the salvage SBRT dose. A divided opinion, after the third round, remained about whether a higher, lower or same dose should be recommended for salvage SBRT compared to the primary treatment. Similarly, disagreement persisted about the fractionation schedule recommended for salvage SBRT. On the other hand, responders reached major agreement about the fact the dose should be prescribed at the isodose. Major agreement was also achieved on the minimum time between primary RT and salvage treatment, set at 2 years.

4. Discussion

Although in the recent years~~,~~ consensus on some critical aspects in PCa RT has been reached [41–44], re-irradiation of intraprostatic recurrence remains disputed. The present ESTRO ACROP study represents one of the first efforts to achieve consensus regarding the use of salvage SBRT for recurrent PCa. Recently, an AIRO survey by Zerini et al. addressed the same issue [25] among Italian radiation

oncologists. The present survey aimed at providing a wider perspective on these controversial aspects by polling international authors of scientific papers on the topic.

Our study showed a consensus or major agreement on 27 out of 40 questions (68% overall), and – if Kendall's coefficient of concordance evaluating consensus among participants for each section of the questionnaire during all rounds is considered - agreement was higher for the items of imaging and staging section, followed by patient selection and SBRT dosimetry sections (very weak agreement). Such difficulty in building solid agreement between the experts answering the questions was also found among the members of the internal committee who were in charge of formulating the questions. In both cases, this was ascribable to the paucity and heterogeneity of data in the literature. As a consequence, the questions' creation was mainly driven by the clinical experience of the physicians. Nevertheless, the virtual debate among members of the internal committee bringing different clinical experience, was fruitful in revealing controversial aspects and in covering all relevant topics related to prostate re-irradiation.

In recent years, the scientific community has shown increasing interest towards re-irradiation of intraprostatic relapse, in particular using a hypofractionated schedule. Indeed, the experts in our study agreed the use of a 5-6 fraction schedule up to a total dose of about 35 Gy (30-35 Gy and > 35 Gy were the most frequently used ones). Importantly, the use of conventional fractionation in re-irradiation may negatively impact disease control, carrying a high risk of treatment-related toxicities [27]. Other factors like large treatment volumes, use of 3-dimensional conformal RT techniques and long follow-up might have also contributed to the findings in the Zilli's series. A study by Zerini et al.[36] assessed SBRT as a feasible approach for local recurrent PCa following a first RT treatment. In this study, no ≥ grade 3 acute or late adverse events were observed with a median follow-up of 21 months, with almost half of the cohort showing no evidence of the disease at that time[36]. These findings have been confirmed in a larger series from the same group[34].

More recent studies confirmed that SBRT represents a safe and effective treatment that may also help in postponing the start of systemic therapies, slowing the course of the disease towards metastatic status [45–47].

In one of latest series of salvage SBRT, Loi et al. [4] observed a 1-year biochemical relapse-free survival rate of 80% and 2 cases of G3 toxicities in a cohort of 50 patients. Similar data were also reported by Jereczek-Fossa et al.[34], Janoray et al.[30], Mbeutcha et al.[21] and Pasquier et al.[22] demonstrating promising results in terms of biochemical control and limited toxicity events. It must be considered however that these data are retrospective and with a short follow-up.

Nevertheless, the limited availability of guidelines, dosimetric indications and instructions for patients' selection hampered the adoption of this therapeutic approach. For this reason ADT is

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currently used in cases of intraprostatic relapse, with RP as the first alternative, even if they are both associated with severe side effects [9,11,48].

The choice of SBRT for PCa recurrences treatment depends upon clinical, dosimetric and imaging-based considerations. As expected, a preliminary evaluation to exclude the presence of metastatic disease is mandatory according to all participants. The temporal span between the first and the salvage RT represents another crucial aspect to take into account before opting for this kind of treatment. In this regard, most panellists agreed that two years should represent the minimum allowed time frame, as earlier recurrences may indicate a low radiosensitivity. Other important factors that inevitably influence the choice of a re-irradiation approach include the patient's response to the first RT course in terms of treatment-related toxicity, as well as his compliance and general health status.

Regarding systemic therapies associated with re-irradiation, consensus was reached about the fact that previous ADT represents no contraindication to a second RT course but at the same time should not be associated with re-irradiation, as one of the purposes of salvage SBRT is to delay the beginning of ADT and the associated cost in terms of QoL[9]. Interestingly, the analogous survey study conducted in Italy reported a tendency of the responders to deliver ADT concomitantly to salvage RT[25], probably in light of the available data in literature about the synergic effect of hormonal therapy and SBRT[19]. However the role of ADT added to salvage SBRT has not been established in largest series[22].

Patient selection is still a matter of debate, as the responders' opinions were divided on maximum T-classification, maximum Gleason score and PSA level for both primary and salvage treatment. The role of biopsy in a re-irradiation scenario after a primary conservative treatment remains controversial. ~~On the contrary, t~~The Uro-GEC-ESTRO study by Kaljouw on B~~R~~T salvage treatment, reported consensus for mandatory histological confirmation before re-irradiation[12]. Histological confirmation before local salvage treatment is mandatory in the guidelines [49,50]. A recent meta-analysis (MASTER 2020) highlighted that, despite difficulties in interpretation, histological confirmation remains important to filter out radiological false positives[15] . On the other hand, in the Italian counterpart of the present study[25], half of responders believe that imaging confirmation of local recurrence such as MRI or PET is enough for diagnosis. In particular, the PICTURE study analysed the diagnostic accuracy of mp-MRI and results suggested that in patients who undergo a repeat prostate biopsy, mp-MRI could be performed to safely avoid this procedure in 14% of cases while obtaining a 97% detection rate of clinically significant PCa[51]. Indeed, in some situations RT is administered based on the imaging findings (for example, metastases–directed RT) or even PSA evolution (salvage RT to prostate bed with or without pelvic lymph node areas). The role of

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confirmation biopsy of the intraprostatic recurrence in era of new generation ~~prostate cancer~~PCa imaging remains to be defined.

Regarding dosimetric considerations, the study highlighted that dose constraints regarding both the CTV and the OARs, including urinary bladder, rectum, femoral heads and penile bulb are still a matter of concern, since no agreement was reached about a recommendable cumulative dose.

Interestingly, regarding the imaging techniques for diagnosis of recurrence, large consensus on choline-PET was achieved, while less than one third responders would recommend PSMA-PET. This imbalance could be explained by the fact that the majority of the studies revealing the potential of PSMA-PET in detecting the site of the lesion and evaluating its extent were published only recently[52], after all rounds of questionnaire were completed.

In the Uro-GEC-ESTRO consensus study, opinion was divided about target volumes (whole gland, partial or focal), whereas in our study the experts' pool reached consensus that the GTV identified on the mp-MRI plus an adaptive margin should be considered as CTV. There is probably more concern for toxicity of SBRT than brachytherapy, although the recent meta-analysis showed the opposite (SBRT had very low GU and GI toxicity)~~.~~[53]. The MASTER study, a recent meta-analysis of 150 studies comparing different local salvage approaches, namely salvage RP, high-intensity focused ultrasound (HIFU), cryotherapy, SBRT, low–dose-rate BT, and HDR BT, demonstrated no significant differences in terms of 5-year recurrence free survival between RP and the other modalities. On the other hand, all RT techniques were associated with lower toxicities profiles, with severe GI toxicities significantly lower with HDR BT compared with RP[15].

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~~5.~~ **Some prospective studies (NCT03438552,** ACTRN12617000035325, NCT00851916)[23,54,55] are currently ongoing regarding SBRT for the treatment of recurrent PCa. **A recent study by Bergamin et al.[55] reported interim results from a small cohort about salvage SBRT on PCa patients, indicating that SBRT can be safely delivered, in selected cases, with a conventional accelerator, broadening the use of salvage SBRT ~~also to RT departments without BRT or CyberKnife facilities~~**. A phase I/II clinical trial by Pasquier et al.[54] is currently ongoing, with the primary objec**tive of finding the recommended dose for salvage SBRT and to estimate the efficacy of such approach. Results from Fuller et al.[23]** suggest that the use **of SBRT as salvage treatment in locally recurrent PCa is possible, with acceptable toxicity and with a good disease-free survival rate at 5 years.** The characteristics of these protocols confirm that complete agreement in the scientific community is still far from being achieved. **As a matter of fact, according to the protocol by Bergamin et al.[55]** a 4-year interval between the first RT course and relapse is required to match inclusion criteria, while Pasquier and Fuller indicate 2-ye**ars as the minimum time frame, as emerged in the present consensus. In addition, these studies also differ on the CTV choice (whole gland irradiation for Fuller et al.[23]** partial irradiation for Pasquier[54], Bergamin et al.[55]). A recent systematic review by Corkum et al.[24] reported no improvement**s in local control** or biochemical recurrence free survival with whole prostate re-RT **with severe late toxicity less frequent with partial prostate re-RT. Moreover, authors suggested that rectal sparing strategies such as endorectal balloons or gel tissue spacers aid in reducing toxicity either with whole gland or focal re-RT. Nevertheless, the study design of these protocols present several features in common, even if a consensus on some of these topics has not been achieved in the present study. For instance, all the studies, according to the current guidelines, require a histologically proven recurrence before the treatment, while our results show a divided opinion about the fact that imaging might be enough for the diagnosis.**

~~6.~~5. Conclusion

To the best of our knowledge, this is the first consensus regarding salvage SBRT for prostate recurrences. The consensus was reached regarding some selection criteria, diagnostic procedures and

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therapeutic indications of salvage SBRT. Interestingly, the main areas where disagreement persists may indicate knowledge gaps for future research. In particular, the role of biopsies, RT dose and OARs constraints remained critical points to be addressed urgently. In the era of personalised medicine and tailored treatments, further activity should focus on evidence which supports best practice. Our ESTRO ACROP Delphi consensus on salvage SBRT may serve as a useful tool to guide the decision-making process and design of trials for this promising approach.

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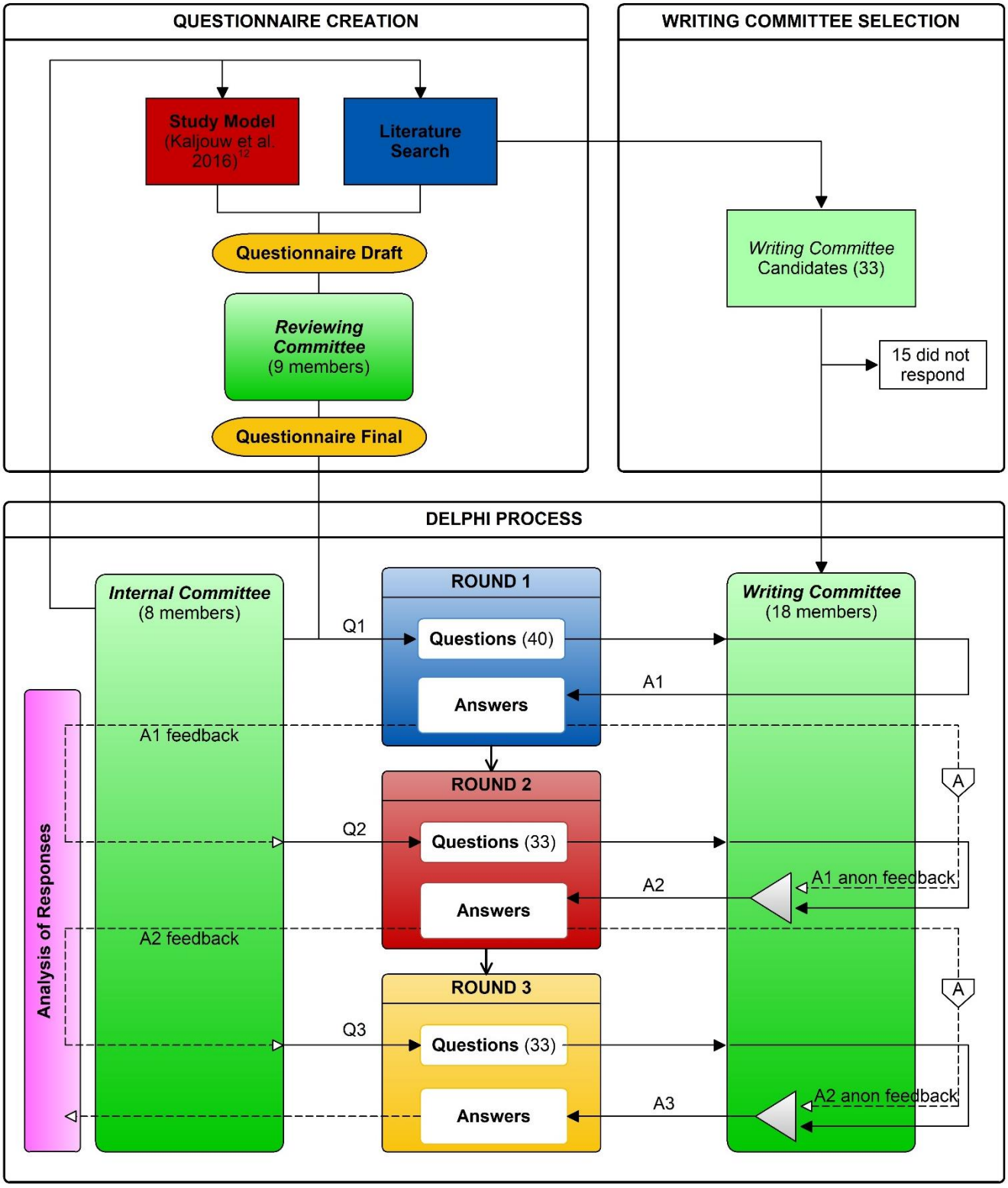
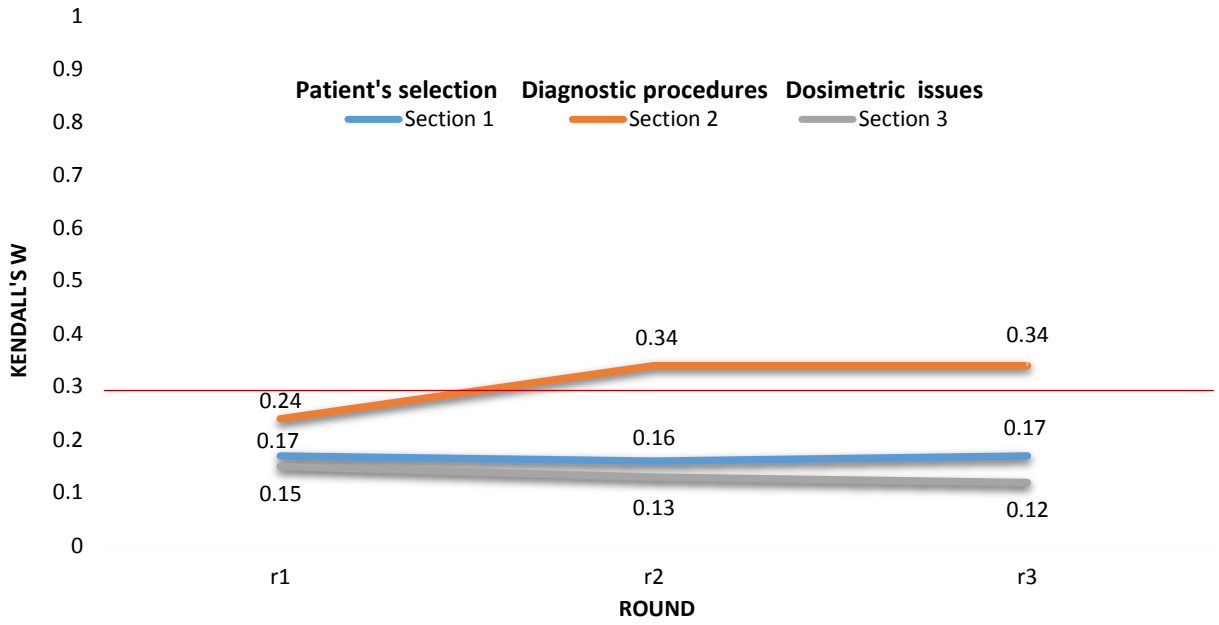
Figure 1. Study design and workflow.



Description. The Figure shows the main steps of the study. The first task, carried out by the *Internal Committee* (IC), consisted in the creation of a questionnaire draft, and was accomplished by readapting the questionnaire of the Uro-GEC-ESTRO study model by Kaljouw et al. 2016[12], on prostate re-irradiation with brachytherapy, in the light of available literature. The literature search was also useful to identity the best candidates to join the *Writing Committee* (WC), as authors of significant scientific papers on the topic. The questionnaire draft was then reviewed and approved by a panel of leading experts on prostate cancer radiotherapy and urology (indicated by EAU), namely the *Reviewing Committee* (RC). The IC was responsible to send the final set of 40 queries (Q1) to the 18 members of the newly formed WC, inaugurating the first round (R1) of the Delphi process. The IC used A1 to adjust questions of next round (Q2) and anonymously sent them as a feedback to the WC before answering the questions of the second round (A2). The same process was repeated for the third round. At each round, responses were collected and analysed.

Figure 2. Evolution of agreement throughout the three rounds for each section according to Kendall coefficient of concordance[36] .



r1/2/3 = round 1/2/3; **Kendall's W** = Kendall Coefficient of Concordance.

Kendall's W ≥ 0.7	Strong agreement
0.3 < Kendall's W < 0.7	Moderate agreement
Kendall's W ≤ 0.3	Weak agreement

Table 1. General information about the writing committee population.

Survey population		*n (%)*
Gender	Male	16 (89)
	Female	2 (11)
Country of work	France	5 (28)
	Italy	8 (44)
	Spain	1 (6)
	Switzerland	2 (11)
	United States	2 (11)
Institution	Private	9 (50)
	Public	9 (50)
Centre specialty (most commonly treated tumor site)*	Breast	14 (87.5)
	Prostate	2 (12.5)
*Number of patients treated per year in your center**	500 - 1000	2 (12.5)
	1000 - 2000	2 (12.5)
	2000 - 3000	6 (37.5)
	> 3000	6 (37.5)

*data not available for 2 responders

Table 2. Summary of the survey results divided in the three sections, the color code indicates the agreement on the topic: green = consensus (agreement > 80%), orange = major agreement (65% < agreement < 80%), red = divided opinion (agreement < 65%).

Initial evaluation

Patients' characteristics

- **No maximum age**
- Exclusion for life expectancy < 5 years
- **Recommended ECOG: 0-1**

Primary treatment

- **Previous ADT represents no contraindication**
- Maximum acceptable T-classification at primary treatment: any T
- Maximum Gleason score at primary treatment: 9-10 (ISUP 5)
- Acceptable PSA at primary treatment: no limit

Salvage treatment

- Maximum acceptable T-classification at secondary treatment: T2
- Maximum Gleason score at salvage treatment: 9-10 (ISUP 5)
- Acceptable PSA at salvage treatment: < 20 ng/dl
- **IPSS should be known**
- Maximum IPSS at salvage: 15
- Should maximal urinary flow (Qmax) be known: not certain
- **Maximum Qmax at salvage: no minimum inferior value**
- Should PVRV be known: not certain
- Maximum PVRV at salvage: no maximum
- **CTV: GTV defined on mpMRI plus adaptive margin**
- No salvage SBRT in case of G2+ urinary/rectal toxicity at primary treatment
- Re-irradiation of seminal vesicles not a contraindication

Diagnostic tests

Metastatic disease

- **Metastatic disease should be evaluated**
- **Imaging for metastatic disease evaluation: Choline-PET**

Biopsy

- For local recurrence imaging (MRI, PET) is enough for diagnosis, no biopsy needed
- MRI-US fusion as imaging device for guiding biopsies
- Number of biopsies at recurrence for whole gland treatment: between 12 and 18
- Number of biopsies at recurrence for partial gland treatment: between 12 and 18
- Gleason score as reliable parameters at re-biopsy: not certain

Salvage treatment

General indications

- **2 years the minimum interval first RT – salvage RT**
- **ADT should not be delivered concomitantly with re-irradiation**
- **Phoenix definition of biochemical relapse is valid for re-treated patients**

Dosimetric considerations – target volume

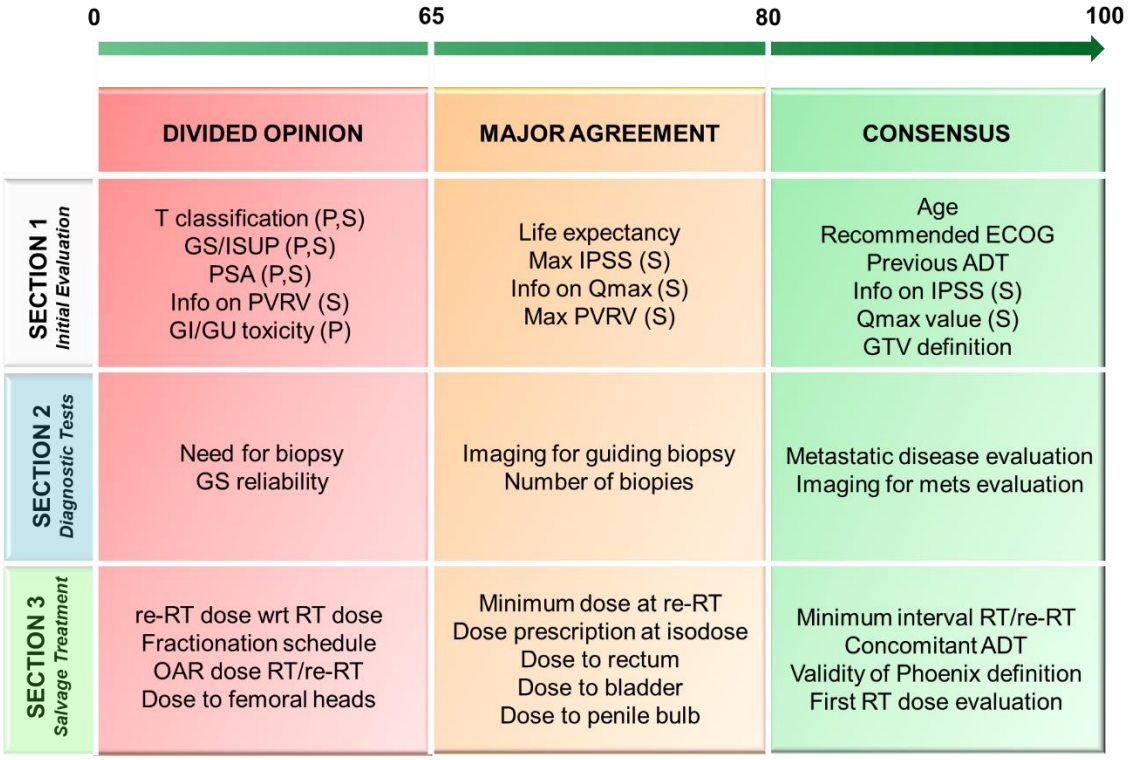
- **Primary treatment dose should be always considered when deciding salvage SBRT dose**
- SBRT dose should be higher respect to the primary treatment dose
- Median EQD2 for effective SBRT with an a/β of 1.5 Gy should be > 35Gy in 5 fractions
- Dose should be prescribed at the isodose with a percentage < 80%
- Recommended fractionation schedule is 35 Gy in 5 fractions

Dosimetric considerations – OARs

- Dose to OARs should be adjusted considering previous dose and time interval between primary and salvage treatment
- Recommended EQD2 range for 2cc of the rectum: 95 – 105 Gy
- Recommended EQD2 range for 2cc of the bladder: 95 – 105 Gy
- Recommended EQD2 range for femoral heads: no maximum
- Recommended EQD2 range for 2cc of the penile bulb: no maximum

List of abbreviations: **CTV** = clinical target volume; **ECOG** = Eastern Cooperative Oncology Group; **EQD2** = 2 Gy equivalent dose; **GTV** = gross tumor volume; **IPSS** = international prostate symptom score; **ISUP** = International Society of Urological Pathology; **mpMRI** = multi-parametric magnetic resonance imaging; **OARs** = organs at risk; **PET** = positron emission tomography; **PVRV** = Post-Voiding Residual Volume; **Qmax** = maximal urinary flow; **RT** = radiotherapy; **SBRT** = stereotactic body RT.

Table 3. Areas of divided opinion (agreement < 65%), major agreement (65% < agreement < 80%), and consensus (agreement > 80%) in the three different sections (Initial Evaluation, Diagnostic Tests, Salvage Treatment) of the questionnaire.



List of abbreviations: **ADT** = androgen deprivation therapy; **ECOG** = Eastern Cooperative Oncology Group; **GI** = gastrointestinal; **GU** = genitourinary; **GS** = Gleason Score; **GTV** = gross tumor volume; **IPSS** = international prostate symptom score; **ISUP** = International Society of Urological Pathology; **mets** = metastases **OAR** = organ at risk; **P** = related to *primary* treatment; **PSA** = prostate-specific antigen; **PVRV** = post-voiding residual volume; **Qmax** = maximal urinary flow; **RT** = radiotherapy; **S** = related to *salvage* treatment; **wrt** = with respect to.

HIGHLIGHTS

- Between 30% and 47% of PCa patients are at risk of intraprostatic recurrence
- ADT, the standard of care, represents a serious burden in terms of QoL
- Purpose of this ESTRO ACROP project is to collect experts' opinion on salvage SBRT
- Low consensus was achieved, highlighting the need for further investigations
- The present Delphi consensus may serve as a practical guidance for salvage SBRT

CONFLICT OF INTEREST STATEMENT

Conflicts of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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REBUTTAL LETTER

To the most appreciated attention of the Editor, Prof. Andres Cervantes, MD, PhD

Cancer Treatment Reviews

Sincerest thanks for your response and reviewer comments on our manuscript that help us to improve it. We hope that a revised version of the manuscript is now suitable for publication on *Cancer Treatment Reviews*.

We have modified the paper in response to the Reviewer's comments, hoping this complies with their remarks.

Here follows a point-by-point description of the changes brought to the manuscript in reply to the Associate Editor's and Reviewer's comments.

Reviewer #1:

This work is on an emerging treatment option in radiorecurrent prostate cancer.

Please check typing and spelling errors.

> **Answer: Thank you for the comment, we have checked the manuscript and corrected typing and spelling errors.**

In the Discussion, I think that some topics deserve more attention. Please add more comments on:

[1] Histological confirmation of disease recurrence, which has been obtained in the majority of published studies in literature about salvage prostate re-irradiation.

[2] The role of mp-MRI in the diagnosis of intra-prostatic radiorecurrence.

[3] Whole-gland re-irradiation, which is usually performed in brachytherapy, and partial irradiation.

> **Answer: Thank you for the suggestions, we have modified the manuscript accordingly**

I suggest to delete or rephrase the sentence about "Cyberknife facilities" in the Discussion (line 3, page 13), because it might be misleading for the reader. I think that cutting-edge techniques, and not a single specific machine, allow safe and effective ablative radiotherapy. It is not a matter of facilities but rather of technique and expertise.

> **Answer: Thank you for the comment, we agree with the Reviewer that the sentence could be misleading and we deleted it.**

Reviewer #2:

The authors report the results of ESTRO-ACROP Delphi Consensus on Salvage stereotactic body radiotherapy (SBRT) for intraprostatic relapse after prostate cancer radiotherapy.

The manuscript is excellent and needs to be published in this prestigious journal.

Moreover, the text is easy to read and the methodology is followed with great precision.

Answer: We would like to thank the Reviewer for the comment and the appreciation of our work.

However some aspects needs to be improved

- Please replace BRT with BT (more used)

Answer: Thank you for the comment, we agree with the fact that BT is the more used abbreviation and we modified the manuscript accordingly.

- The conclusions of the Systematic Review and Meta-analysis of Local Salvage Therapies After Radiotherapy for Prostate Cancer (MASTER) (Eur Urol 2020), cited in the discussion, needs to better show and totally explained, moreover, in the introduction and in the discussion the role of BT in this setting should be better discussed

Answer: Thank you for the suggestion, we discussed more in depth the MASTER study and the role of BT in the discussion section.

- In the discussion the role of prostate-rectum spacer should be discussed in terms of benefit for toxicity

Answer: Thank you for the comment, the manuscript has been modified accordingly.