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
BT	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
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

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 (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 (BT) 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 approaches, in particular re-irradiation with high dose-rate (HDR) BT, as it was associated with lower severe GU and GI toxicities, without compromising the oncological outcome[15]. In a similar manner, a systematic review endorsed by 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 BT for locally recurrent PCa after EBRT (NRG/RTOG 0526) [17], no further definitive data are currently available concerning the use of BT as a salvage option for recurrent PCa. A recent Uro-GEC-ESTRO (Groupe Euopéen de Curiethérapie – European Society for Radiotherapy and Oncology) consensus study by Kaljouw et al. [12], investigating expert opinion on salvage BT, 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 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 BT 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,

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

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, 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. 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 [34] (Zilli et a. 2016). 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.[32] 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[32]. These findings have been confirmed in a larger series from the same group[30] (Jereczek-Fossa et al., 2019).

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.[30], Janoray et al.[37], 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 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. The Uro-GEC-ESTRO study by Kaljouw on BT 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 the biopsy 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 confirmation biopsy of the intraprostatic recurrence in era of new generation 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 mpMRI 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]. 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. A phase I/II clinical trial by Pasquier et al.[54]is currently ongoing, with the primary objective 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-years 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 improvements 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.

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 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.

References

1 Center MM, Jemal A, Lortet-Tieulent J, *et al.* International variation in prostate cancer incidence and mortality rates. Eur. Urol. 2012; **61**: 1079–92.

2 Artibani W, Porcaro AB, De Marco V, Cerruto MA, Siracusano S. Management of Biochemical Recurrence after Primary Curative Treatment for Prostate Cancer: A Review. Urol. Int. 2018; **100**: 251–62.

3 Hamdy FC, Donovan JL, Lane JA, *et al.* 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. *N Engl J Med* 2016; **375**: 1415–24.

4 Loi M, Di Cataldo V, Simontacchi G, *et al.* Robotic Stereotactic Retreatment for Biochemical Control in Previously Irradiated Patients Affected by Recurrent Prostate Cancer. *Clin Oncol* 2018; **30**: 93–100.

5 Créhange G, Roach M, Martin, *et al.* Salvage reirradiation for locoregional failure after radiation therapy for prostate cancer: Who, when, where and how? Cancer/Radiotherapie. 2014; **18**: 524–34.

6 Tetreault-Laflamme A, Crook J. Options for Salvage of Radiation Failures for Prostate Cancer. Semin. Radiat. Oncol. 2017; **27**: 67–78.

7 Alongi F, De Bari B, Campostrini F, *et al.* Salvage therapy of intraprostatic failure after radical external-beam radiotherapy for prostate cancer: A review. Crit. Rev. Oncol. Hematol. 2013; **88**: 550–63.

8 Zargar H, Lamb AD, Rocco B, *et al.* Salvage robotic prostatectomy for radio recurrent prostate cancer: Technical challenges and outcome analysis. Minerva Urol. e Nefrol. 2017; **69**: 26–37.

9 Bomers JGR, Overduin CG, Jenniskens SFM, *et al.* Focal Salvage MR Imaging–Guided Cryoablation for Localized Prostate Cancer Recurrence after Radiotherapy: 12-Month Follow-up. *J Vasc Interv Radiol* 2020; **31**: 35–41.

10 Matei DV, Ferro M, Jereczek-Fossa BA, *et al.* Salvage radical prostatectomy after external beam radiation therapy: A systematic review of current approaches. Urol. Int. 2015; **94**: 373–82.

11 Mohler JL, Antonarakis ES, Armstrong AJ, *et al.* Prostate cancer, version 2.2019. *JNCCN J Natl Compr Cancer Netw* 2019; **17**: 479–505.

12 Kaljouw E, Pieters BR, Kovács G, Hoskin PJ. A Delphi consensus study on salvage brachytherapy for prostate cancer relapse after radiotherapy, a Uro-GEC study. *Radiother Oncol* 2016; **118**: 122–30.

13 Ingrosso G, Becherini C, Lancia A, *et al.* Nonsurgical Salvage Local Therapies for Radiorecurrent Prostate Cancer: A Systematic Review and Meta-analysis. Eur. Urol. Oncol. 2020; **3**: 183–97.

14 Bachmann N, Riggenbach E, Elicin O, Shelan M. Extremely hypofractionated salvage radiotherapy for isolated local recurrent prostate cancer: toxicity and biochemical control. *23rd Annu SASRO Meet* 2019.

15 Valle LF, Lehrer EJ, Markovic D, *et al.* A Systematic Review and Meta-analysis of Local Salvage Therapies After Radiotherapy for Prostate Cancer (MASTER). Eur. Urol. 2020. DOI:10.1016/j.eururo.2020.11.010.

16 Munoz F, Fiorica F, Caravatta L, *et al.* Outcomes and toxicities of re-irradiation for prostate cancer: A systematic review on behalf of the Re-Irradiation Working Group of the Italian Association of Radiotherapy and Clinical Oncology (AIRO). Cancer Treat. Rev. 2021; **95**. DOI:10.1016/j.ctrv.2021.102176.

17 Crook JM, Zhang P, Pisansky TM, *et al.* A Prospective Phase 2 Trial of Transperineal Ultrasound-Guided Brachytherapy for Locally Recurrent Prostate Cancer After External Beam Radiation Therapy (NRG Oncology/RTOG-0526). *Int J Radiat Oncol Biol Phys* 2019; **103**: 335–43.

18 Fuller DB, Wurzer J, Shirazi R, Bridge SS, Law J, Mardirossian G. High-dose-rate stereotactic body radiation therapy for postradiation therapy locally recurrent prostatic carcinoma: Preliminary prostate-specific antigen response, disease-free survival, and toxicity assessment. *Pract Radiat Oncol* 2015; **5**: e615–23.

19 Leroy T, Lacornerie T, Bogart E, Nickers P, Lartigau E, Pasquier D. Salvage robotic SBRT for local prostate cancer recurrence after radiotherapy: Preliminary results of the Oscar Lambret Center. *Radiat Oncol* 2017; **12**: 1–7.

20 Arcangeli S, Gambardella P, Agolli L, *et al.* Stereotactic body radiation therapy salvage

reirradiation of radiorecurrent prostatic carcinoma relapsed in the prostatic bed. *Tumori* 2015; **101**: e57–9.

21 Mbeutcha A, Chauveinc L, Bondiau PY, *et al.* Salvage prostate re-irradiation using high-dose-rate brachytherapy or focal stereotactic body radiotherapy for local recurrence after definitive radiation therapy. *Radiat Oncol* 2017; **12**. DOI:10.1186/s13014-017-0789-9.

22 Pasquier D, Martinage G, Janoray G, *et al.* Salvage Stereotactic Body Radiation Therapy for Local Prostate Cancer Recurrence After Radiation Therapy: A Retrospective Multicenter Study of the GETUG. *Int J Radiat Oncol Biol Phys* 2019; **105**: 727–34.

23 Fuller D, Wurzer J, Shirazi R, *et al.* Retreatment for Local Recurrence of Prostatic Carcinoma After Prior Therapeutic Irradiation: Efficacy and Toxicity of HDR-Like SBRT. *Int J Radiat Oncol Biol Phys* 2020; **106**: 291–9.

24 Corkum MT, Mendez LC, Chin J, D'Souza D, Boldt RG, Bauman GS. A Novel Salvage Option for Local Failure in Prostate Cancer, Reirradiation Using External Beam or Stereotactic Radiation Therapy: Systematic Review and Meta-Analysis. *Adv Radiat Oncol* 2020; published online May 12. DOI:10.1016/j.adro.2020.04.022.

25 Zerini D, Jereczek-Fossa BA, Ciabattoni A, *et al.* PROLAPSE: survey about local prostate cancer relapse salvage treatment with external beam re-irradiation: results of the Italian Association of Radiotherapy and Clinical Oncology (AIRO). *J Cancer Res Clin Oncol* 2020. DOI:10.1007/s00432-020-03297-5.

26 Hsu C-C, Sandford BA. The Delphi Technique: Making Sense of Consensus. 2007.

27 Detti B, Bonomo P, Masi L, *et al.* CyberKnife stereotactic radiotherapy for isolated recurrence in the prostatic bed. *World J Urol* 2016; **34**: 311–7.

28 Shelan M, Abo-Madyan Y, Welzel G, *et al.* Dose-escalated salvage radiotherapy after radical prostatectomy in high risk prostate cancer patients without hormone therapy: Outcome, prognostic factors and late toxicity. *Radiat Oncol* 2013; **8**. DOI:10.1186/1748-717X-8-276.

29 D'Agostino GR, Di Brina L, Mancosu P, *et al.* Reirradiation of Locally Recurrent Prostate Cancer With Volumetric Modulated Arc Therapy. *Int J Radiat Oncol Biol Phys* 2019; **104**: 614–21.

30 Jereczek-Fossa BA, Rojas DP, Zerini D, *et al.* reirradiation for isolated local recurrence of prostate cancer: Mono-institutional series of 64 patients treated with salvage stereotactic

body radiotherapy (SBrT). *Br J Radiol* 2019; **92**. DOI:10.1259/bjr.20180494.

31 Rutenberg MS, Meister M, Amin PP, Hussain A, Naslund MJ, Kwok Y. Salvage external beam radiotherapy for locally recurrent prostate cancer after definitive brachytherapy. In: Brachytherapy. Elsevier Inc., 2016: 722–9.

32 Zerini D, Jereczek-Fossa BA, Fodor C, *et al.* Salvage image-guided intensity modulated or stereotactic body reirradiation of local recurrence of prostate cancer. *Br J Radiol* 2015; **88**. DOI:10.1259/bjr.20150197.

33 Scher N, Bauduceau O, Bollet M, *et al.* stereotactic prostate focal reirradiation therapy for local recurrence: preliminary results of hartmann Oncology radiotherapy group. 2019.

34 Zilli T, Benz E, Dipasquale G, Rouzaud M, Miralbell R. Reirradiation of Prostate Cancer Local Failures After Previous Curative Radiation Therapy: Long-Term Outcome and Tolerance. *Int J Radiat Oncol Biol Phys* 2016; **96**: 318–22.

35 Lee SH, Jung J, Chang SG. Salvage helical tomotherapy for prostate cancer recurrence following definitive external beam radiotherapy: A case report. *Oncol Lett* 2015; **10**: 1044–6.

36 Dipasquale G, Zilli T, Fiorino C, Rouzaud M, Miralbell R. Salvage reirradiation for local failure of prostate cancer after curative radiation therapy: Association of rectal toxicity with dose distribution and normal-tissue complication probability models. *Adv Radiat Oncol* 2018; **3**: 673–81.

37 Janoray G, Reynaud-Bougnoux A, Ruffier-Loubière A, Bernadou G, Pointreau Y, Calais G. Ré-irradiation stéréotaxique robotisée de récidive locale de cancer de prostate après radiothérapie externe : résultats préliminaires. *Cancer/Radiotherapie* 2016; **20**: 275–81.

38 Marozzi M. Testing for concordance between several criteria. *J Stat Comput Simul* 2014; **84**: 1843–50.

39 Taylor RM, Feltbower RG, Aslam N, Raine R, Whelan JS, Gibson F. Modified international e-Delphi survey to define healthcare professional competencies for working with teenagers and young adults with cancer. *BMJ Open* 2016; **6**: 1–12.

40 Roach M, Hanks G, Thames H, *et al.* Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: Recommendations of the RTOG-ASTRO Phoenix Consensus Conference. *Int J Radiat Oncol Biol Phys* 2006; **65**: 965–74.

41 Ghadjar P, Fiorino C, Munck af Rosenschöld P, Pinkawa M, Zilli T, van der Heide UA. ESTRO ACROP consensus guideline on the use of image guided radiation therapy for localized prostate cancer. *Radiother Oncol* 2019; **141**: 5–13.

42 Salembier C, Villeirs G, De Bari B, *et al.* ESTRO ACROP consensus guideline on CT- and MRI-based target volume delineation for primary radiation therapy of localized prostate cancer. *Radiother Oncol* 2018; **127**: 49–61.

43 Hoskin PJ, Colombo A, Henry A, *et al.* GEC/ESTRO recommendations on high dose rate afterloading brachytherapy for localised prostate cancer: An update. Radiother. Oncol. 2013; **107**: 325–32.

44 Lam TBL, MacLennan S, Willemse PPM, *et al.* EAU-EANM-ESTRO-ESUR-SIOG Prostate Cancer Guideline Panel Consensus Statements for Deferred Treatment with Curative Intent for Localised Prostate Cancer from an International Collaborative Study (DETECTIVE Study). Eur. Urol. 2019; **76**: 790–813.

45 Arcangeli S, Agolli L, Donato V. Retreatment for prostate cancer with stereotactic body radiation therapy (SBRT): Feasible or foolhardy? Reports Pract. Oncol. Radiother. 2015; **20**: 425–9.

46 Cuccia F, Nicosia L, Mazzola R, *et al.* Linac-based SBRT as a feasible salvage option for local recurrences in previously irradiated prostate cancer. *Strahlentherapie und Onkol* 2020; published online May 12. DOI:10.1007/s00066-020-01628-6.

47 Olivier J, Basson L, Puech P, *et al.* Stereotactic re-irradiation for local recurrence in the prostatic bed after prostatectomy: Preliminary results. *Front Oncol* 2019; **9**. DOI:10.3389/fonc.2019.00071.

48 D'Amico A V, Cote K, Loffredo M, Renshaw AA, Schultz D. Determinants of prostate cancer-specific survival after radiation therapy for patients with clinically localized prostate cancer. *J Clin Oncol* 2002; **20**: 4567–73.

49 EAU Guidelines: Prostate Cancer | Uroweb. 2020. https://uroweb.org/guideline/prostate-cancer/ (accessed Sept 30, 2020).

50 NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer. 2020.

51 Simmons LAM, Kanthabalan A, Arya M, *et al.* The PICTURE study: diagnostic accuracy of multiparametric MRI in men requiring a repeat prostate biopsy. 2017; **116**.

DOI:10.1038/bjc.2017.57.

52 Kishan AU, Nickols NG, Spratt DE. Prostate-specific Membrane Antigen Positron Emission Tomography–guided Radiotherapy. Eur. Urol. Focus. 2020. DOI:10.1016/j.euf.2020.09.020.

53 Valle LF, Lehrer EJ, Markovic D, *et al.* A Systematic Review and Meta-analysis of Local Salvage Therapies After Radiotherapy for Prostate Cancer (MASTER). *Eur Urol* 2020; **1**: 1–13.

54 Pasquier D, Le Deley MC, Tresch E, *et al.* GETUG-AFU 31: A phase I/II multicentre study evaluating the safety and efficacy of salvage stereotactic radiation in patients with intraprostatic tumour recurrence after external radiation therapy-study protocol. *BMJ Open* 2019; **9**. DOI:10.1136/bmjopen-2018-026666.

55 Bergamin S, Eade T, Kneebone A, *et al.* Interim Results of a Prospective Prostate-Specific Membrane Antigen-Directed Focal Stereotactic Reirradiation Trial for Locally Recurrent Prostate Cancer. *Int J Radiat Oncol Biol Phys* 2020; published online July 11. DOI:10.1016/j.ijrobp.2020.07.014.