Review Article

Adaptive radiotherapy for nasopharyngeal carcinoma

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Abstract: The concept of "adaptive radiotherapy" (ART) was introduced more than 20 years ago. It refers to imaging feedback control strategies with treatment plan modification in response to patient-specific treatment variation during the course of radiotherapy. ART is particularly relevant to nasopharyngeal carcinoma (NPC) patients in the precision radiotherapy era since contemporary intensity-modulated radiotherapy (IMRT) combined with chemotherapy could result in significant volumetric alteration of the tumor and normal tissue during the treatment course. Studies have shown that ART could enhance locoregional control (LRC) and improve patients' functional outcomes. ART has been evaluated in clinical research and implemented in clinical practice to improve IMRT customization for patients in need. However, no consensus exists regarding when and how to implement ART in a systematic manner. ART is often restricted by its labor-intensive and time-consuming nature and technical challenges. This review summarizes recent advances in the implementing ART for NPC relating to potential dosimetric and clinical benefit, when and how to trigger ART, efforts to streamline the workflow of ART including image registration, and potential integration of computer-assisted auto-contouring.

Keywords: Intensity-modulated radiotherapy (IMRT); nasopharyngeal carcinoma (NPC); adaptive radiotherapy (ART); replanning; deformable registration; auto-segmentation

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Introduction

Intensity-modulated radiotherapy (IMRT) has become the standard treatment for nasopharyngeal carcinoma (NPC) in the precision radiotherapy era (1). It enables the delivery of highly conformal dose distribution to target volumes with superior normal tissue sparing (2). However, IMRT is often delivered on a single snapshot of the patient's anatomy and position and does not take into account the potential changes occurring during a typical 7-week treatment course. With very steep dose fall-off at strategic locations around target volumes in NPC IMRT, significant target shrinkage and anatomical changes during the course of the treatment could increase the risk of geographical target miss and organs-at-risk (OARs) overdose (3,4). Data (5) have shown that systematic strategies addressing these patient-specific changes during a course of radiotherapy are particularly important for NPC due to its radio-/chemo-sensitive nature, proximity to multiple OARs, as well as limited salvage options in the event of subsequent local failure.

The concept of "adaptive radiotherapy" (ART) was introduced by Yan *et al.* in 1997 (6,7) as an imaging feedback control strategy with treatment plan modification in response to patient-specific treatment variation during

the course of radiotherapy. It generally includes the following four steps: (I) treatment dose assessment, (II) treatment variation identification/evaluation, (III) treatment modification decisions, and (IV) adaptive treatment modification (8). Theoretically, ART can be employed on a daily basis to correct for any dose discrepancy from the original IMRT plan. However, in practice, ART strategies are often only implemented in selected cases at certain times. In part, this is due to the labor-intensive and time-consuming nature of the current ART processes. Identifying who may benefit from ART and when/how to implement ART remain active research areas. Significant progress has been made in recent years to improve and streamline the ART process for NPC in the clinical setting. This review summarizes recent advances in the implementation of ART for NPC relating to potential dosimetric and clinical benefits, how to trigger its use before or during the radiotherapy course, and efforts in streamlining ART such as improving deformable registration algorithms and refining computer-assisted auto-contouring tools.

Classification of ART

ART can be classified as reactive and proactive based on whether it is part of the initial treatment package. An example of reactive ART includes re-scan and re-plan to counter unstable treatment setup or significant observed anatomic changes caused by tumor shrinkage, weight loss, or internal motion. Proactive ART often incorporates re-planning as a part of the initial treatment package in anticipating significant tumor and normal tissue changes at certain time points. ART can be implemented for different purposes. To describe the ART intent, the following nomenclature has been proposed by Heukelom *et al.* (9): (I) ART_{ex_aequo}—serial plan verification to ensure initial plan parameters are maintained for tumor and OARs, (II) ART_{OAR}—reduced OAR dose with the same initial plan dosimetry to CTV, (III) ART_{amplio}—increased dose to tumor with isotoxic or lower OAR dose, (IV) ART_{reduce}—"shrinking CTV" for on-treatment responders, and (5) ART_{totale}—increase dose to sub-volume of initial CTV.

Necessity and benefits of ART

Many NPC patients can experience significant weight loss during the 6 to 7 weeks of radiotherapy. Patients having significant weight loss tend to be accompanied by reduced skin separation at various levels of the cervical spine and neck, causing significant inter-fractional setup instability. Excessive weight loss and tumor shrinkage may result in a significant deviation of accumulated delivered dose from the initially planned dose. Studies (10,11) have shown that these volumetric and geographic variations could compromise the conformality of IMRT plans and increase the dose to selected OARs. A prospective study of 19 NPC patients by Cheng *et al.* (11) evaluated volumetric and dosimetric changes during IMRT. Patients were rescanned at the 30 and 50 Gy time-points, and hybrid plans were generated by recontouring target volumes and OARs followed by applying the parameters of the original plan to the newly acquired CT at these two time-points. The authors reported a mean weight loss of 5.4% and 9.3%, a mean 9% and 16% reduction of gross tumor volume (GTV), and a mean volume reduction of the contralateral parotid gland by 0.7 and 3.4 cm^3 and of the ipsilateral parotid by 5.3 and 8.4 cm^3 at the 30 and 50 Gy dose points in the course, respectively. Compared to the original plan, the hybrid plan showed a significantly higher dose with greater dose inhomogeneity in most target volumes, and a higher maximum dose to the spinal cord and brainstem, as well as a higher mean dose to parotid glands.

The dosimetric and clinical benefits of ART in NPC have been demonstrated in several prospective and retrospective studies (4,10-19) (*Table 1*). Emerging data (12,13,15,17,19,20) have shown that adaptation of the treatment plan can result in improved target coverage and homogeneity, reduced dose maximum to critical structures like the spinal cord and brainstem, as well as volume reductions in target volumes and lower accumulated doses to parotid glands.

In addition to these dosimetric benefits, the clinical benefit of ART has been shown in several studies. Limited data suggest that ART has the potential to reduce normal-tissue toxicities and enhance locoregional control (LRC) although there is no significant difference in distant control and overall survival (4,16,18). A non-randomized prospective controlled cohort study by Yang *et al.* (18) showed that IMRT replanning improved quality of life and enhanced LRC in patients with NPC. However, the authors did not report the details regarding how the replanning was triggered. A propensity score-matched analysis conducted by Luo *et al.* (16) compared the outcome of T3-T4 NPC patients with (n=66) *vs.* without (n=66) replanning. The decision for replanning was made at the physician's discretion and considered multiple factors such as proximity of GTV to critical OARs, significant weight loss, declining

Table 1 Selected studies on dosimetric and clinical benefit of adaptive radiotherapy in NPC

Author, year, No. of Pts	Methodology	Findings
Studies addressing the dosimetric need for ART		
Bahl, 2019 (14), N=20	• Repeat planning CT and MRI at 17th fraction	• Mean (SD) weight loss at 17th fx *vs.* baseline: 3.4±2.6 kg
	• ART plan was generated	• Mean neck diameter at C2 level: 13.3 (*vs.* baseline: 14.2±1.02 cm, P=0.001)
		• GTV70 volume loss: 29.2%
		• Median dose to right parotid gland by 7.7 Gy (P=0.054)
		• Median dose to left parotid gland by 7.2 Gy (P=0.016)
		• Mean weight loss is statistically correlated with increased dose to right parotid (P=0.043) and left parotid (P=0.024)
Cheng, 2012 (11), N=19	• Repeat planning CT and MRI at 30 and 50 Gy (14th and 24th fractions)	• Mean weight loss at 30 and 50 Gy were: 5.4% and 9.3%
	• Hybrid plans were generated by superimposing the original plan to the repeat CT at 30 Gy (HPLAN30) and 50 Gy (HPLAN50)	• Vmean of GTV_NP and GTV_N: ↓ by 9% (P=0.001) and 16% (P=0.007) in the HPLAN30 and ↓ by 13% (P=0.002) and 29% (P=0.026) in the HPLAN50
		• Dmean and D95 of all target volumes: slightly for both HPLAN30 and HPVLAN50
		• Dmax, Dmean, Dmedian, and D01 of various OARs:
Mnejja, 2020 (10), N=20	• Repeat CT at 19th fraction (38 Gy) and GTV, PTV was recontoured	Hybrid plan *vs.* original plan:
	• A hybrid plan was generated on the new CT using the same parameter of the original plan	• GTV-p and GTV-n: ↓ by 29.5% and 58.6%
		• High/intermediate/low-dose PTV: ↓ by 34.4%/17.0%/11.6%
		• D98% of high/intermediate/low-dose PTVs: ↓ by 1.4/0.3/1.2 Gy
		• Dmax by 0.76 Gy (1.08% of the prescribed dose), P=0.009
		• Reduction of conformality index in the order of 0.02 and 0.01
		• No correlation of change of PTV coverage with T-category
		• Coverage of low dose PTV was correlated with N-category

Table 1 (*Continued*)

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Author, year, No. of Pts	Methodology	Findings
Studies showing dosimetric benefits of ART		
Chitapanarux, 2015 (12), N=17	• The second CT scan acquired at 17th fraction, and an adapted plan was generated	Volume changes in the adapted plan *vs.* hybrid plan:
	• Implemented the adapted plan after 20th fraction	• Mean volume of the ipsilateral parotid: ↓ by 6.1 cm^3 (31%)
	• A hybrid plan was generated by applying the optimization parameters of the original plan to the anatomy of the second CT	• Mean volume of the contralateral parotid: ↓ by 5.4 cm^3 (24%)
		Dosimetric changes in the adapted plan *vs.* hybrid plan:
		• Dmin and homogeneity of all PTVs. increased
		• Dmax of spinal cord: ↓ in 94% of the pts (1.6–5.9 Gy, P<0.001)
		• Dmax of brainstem: ↓ in 94% if the pts (2.1–9.9 Gy, P<0.001)
		• Dmean of contralateral parotid: ↓ in 70% of the pts (0.2–4.4 Gy)
Deng, 2017 (15), N=20	• Repeat CT at 5th and 15th fractions, and adaptive replans were generated and delivered	Adaptive plan *vs.* hybrid plan:
	• Hybrid plan 1 and 2: super-imposing original plan on the new CT acquired at the 5th and 15th fractions	• Improved conformity index for PTVs. and CTVs
		• Tumor coverage:
		• Dmax to the brainstem and temporal lobes: ↓
		• Dmean to glottis: ↓
		• V50 for supraglottis: ↓
		• Dmean and V30 for left parotid: ↓
Hu, 2018 (20), N=40	• 40 IMRT in 2013-2015	Volume reduction in the adapted plan *vs.* hybrid plan:
	• The second CT scan captured at the 22nd fraction	• Mean volume of the ipsilateral parotid: 23 *vs.* 19 cc, P<0.001
		• Mean volume of contralateral parotid: 23 *vs.* 18 cc, P<0.001
		• Mean volume of CTV-1: 32 *vs.* 21 cc, P<0.001
		• Mean volume of PTV-1: 126 *vs.* 107 cc, P<0.001
		• ART has a dosimetric benefit for patients with a heavy initial weight, large BMI, obvious weight loss, concurrent chemo-radiotherapy, and stages III-IV.

Table 1 (*Continued*)

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Author, year, No. of Pts	Methodology	Findings
Lu, 2014 (19), N=12	• The second CT [CT2] scan acquired at 25th fraction	Hybrid plan *vs.* original plan:
	• Hybrid IMRT plan was generated by deforming doses of original plan to CT2	• Mean neck diameter at the centre of odontoid process: 14.4±1.1cm (*vs.* baseline: 15.4±1.0 cm, P<0.005)
	• Adaptive plan was generated by replanning on CT2	• Mean volume of the right and left parotid glands significantly decreased by (24.6±11.9)% and (35.1±20.1)%, respectively
		• Tumor coverage: ↓
		• Dmax to the brainstem and spinal cord: in 8/12 patients
		Adaptive plan *vs.* hybrid plan:
		• Tumor coverage and ↓Dmax to the brainstem and temporal lobes
Wang, 2010 (17), N=28	• Repeat CT at 25th fraction, and an adaptive plan was generated	ART plan *vs.* original plan:
		• Prescription dose delivered to the CTV1: by 4.9%±10.9%
		• Dmax to the spinal cord: ↓ by 5.0±9.2 Gy
		• Dmean to left parotid: ↓ by 4.2±10.0 Gy
		• V30 to right parotid: ↓ by 11.5%
Studies showing clinical benefits of ART		
Luo, 2017 (16), N=132	• 132 IMRT in T3-T4 NPC treated between 2004–2010	Replanning *vs.* no replanning
	◆ 66 with replanning	• higher 5-year LRC: 96.7% *vs.* 88.1%, P=0.022
	◆ 66 without replanning (matching cohort)	• No significant difference in DC and OS
	• The 1st replan implemented at a median dose of 44 Gy (8.8–60.0 Gy) (22nd fraction)	• Multivariable analysis: replanning is an independent prognostic factor for LRC (HR 0.23, P=0.028)
	• Median 2 [1–3] replanning	
Yang, 2013 (18), N=129	• 129 IMRT in 2007–2011	Replanning *vs.* no replanning:
	◆ 43 without replanning	• Much improved global QoL and other QoL scales
	◆ 86 with replanning	• Significantly higher 2-year LRC (97.2% *vs.* 92.4%, P=0.040)
		• No significant OS difference (2-years: 89.8% *vs.* 82.2%, P=0.475)

Table 1 (*Continued*)

Table 1 (*Continued*)

Author, year, No. of Pts	Methodology	Findings
Zhao, 2011 (4), N=175	• 175 IMRT in 2002–2007	Replanning *vs.* no replanning:
	• 158 with obvious anatomic changes before 20th fraction:	• Improved LC in T3-4 patients
	◆ 33 repeat CT/re-planned	• No difference in OS
	◆ 66 without re-planning (matching cohort)	

No. of Pt, number of patients; ART, adaptive radiotherapy; Pt, patients; S, standard deviation; LC, local control; LRC, locoregional control, OS, overall survival; LRFS, regional recurrence-free survival; DMFS, distant metastasis-free survival; OAR, organ-at-risks; D95, dose to 95% of volume; PTV, planning target volume; GTV, gross tumor volume; CTV, clinical target volume; CTV-1, clinical target volume, representing tissues with high risk of harboring microscopic disease; CTV-N, gross tumor volume of metastatic lymph nodes; BMI, body mass index.

nutritional status, significant changes in tumor size and an ill-fitting mask, as well as severe acute toxicities. An average of two new ART plans (range, 1–3) was implemented. The time from re-simulation to implementation of the new plan was generally 1–3 days. The study showed that the replanning cohort had a higher LRC compared to the cohort without replanning, and the effect of replanning on LRC remained after adjusting for confounders. Distant metastasis rates were similar and remained the main pattern of treatment failure for both cohorts. No significant survival advantage was observed with ART.

Practical aspects of ART—triggers and timing

To incorporate ART into routine clinical practice, one needs to consider who would benefit from ART, and when to implement it. The latter often need to take into account any substantial volumetric changes that warrant ART and whether sufficient time remains in the treatment course to derive benefit from the adaptation.

Reasons or "triggers" for ART vary between studies (*Table 2*) (16,21-26). There is also no consensus regarding the optimal time to implement ART, and the "threshold" or "trigger" to mandate it. For reactive ART to account for time-dependent changes, triggered adaptations are frequently applied. Triggered adaptation refers to the process of adapting the treatment plan when exceeding a certain "threshold", such as when a patient experiences considerable shrinkage of gross tumor or anatomical changes related to weight loss. Yao *et al.* (25) evaluated real-time volumetric and dosimetric changes in the parotid gland to determine the optimal replanning criteria ("trigger") and timing for parotid protection-based adaptive IMRT in NPC. They suggested that when two out of the three following parameters reach their cut-off, an ART should be considered: (I) initial parotid volume >52.8 cm^3, (II) initial parotid mean dose >32 Gy, and (III) weight loss rate >2.3% at the 11th fraction or >3.6% at the 16th fraction, or >4.4% at the 21st fraction. In Huang *et al.*'s study (24), each patient had repeated CT scans after every five fractions and at treatment completion. They used auto-segmentation to re-contour the targets and OARs and performed deformable registration for CT-CT fusion. Two replans at the 5th and 15th fractions were suggested since significant volumetric changes occurred around these two time points.

The impact of anatomic change on actual delivered dose is highly patient-dependent and appears to affect OAR sparing (e.g., parotid) to a relatively greater extent compared

Table 2 Suggested timing and triggers for ART in selected studies

Author, year, No. of Pts	Triggers	Timing
Bhide, 2010 (21), N=20	Significant volumetric changes and dosimetric deviation in the tumor volumes and OARs	Week 2 of RT
Brown, 2016 (22), N=110	For re-CT: Significant anatomical changes For replanning: OAR's receiving a higher than acceptable dose and/ or inadequate target volume coverage	Week 3 for NPC and week 4 for OPC with large neck nodes
Gai, 2017 (23), N=13	Significant shrinkage of GTV (≥50%) and/or parotid Dmean increase by 10% compared to initial plan	Between 21st to 25th fractions
Huang, 2015 (24), N=19	Significant dosimetric deviation	Two replans at the 5th and 15th fractions were suggested
Luo, 2017 (16), N=132	Physicians discretion: weight loss, nutritional status, changes in tumor size, an ill-fitting mask and extent of acute reactions	The 1st replan implemented at a median dose of 44 Gy (8.8–60.0 Gy) (22nd fractions)
Yao, 2015 (25), N=50	Two out of 3 parameters reached the cut-off values (based on the possibility of overdosing the parotid): • Initial parotid volume >52.8 cm^3 • Initial parotid Dmean >32 Gy • Weight loss rate >2.3% at 11th fraction or >3.6% at 16th fractions or >4.4% at 21st fraction	Assessing the weight loss rate at 11th, 16th or 21st fractions
Yu, 2019 (26), N=70	• Body weight loss >10% • Significant increase of high dose area over neck skin • Insufficient dose coverage over neck nodal targets • Increase risk of overdosing spinal cord • Uncorrectable setup variations • Part of target volume outside of body contour • Increased risk of overdosing optic chiasm	Mostly during week 4–5 and after 20th fractions

No. of Pt, number of patients; OAR, organ-at-risks; GTV, gross tumor volume; re-CT, repeat CT simulation; Dmean, mean dose to parotid.

to the impact on GTV coverage (27). A prospective study of weekly volumetric changes during chemoradiation on 20 head and neck cancer patients (4 were NPC) from Bhide *et al* (21) showed that the most significant volumetric and dosimetric alteration occurred at week 2 of IMRT. There was a significant parotid volume reduction by week 2 (15%, P<0.001) and week 4 (31%) (both P<0.001), and an increment of the mean dose to the ipsilateral parotid gland at week 4 of IMRT (2.7 Gy, P=0.006). For NPC patients with large nodes receiving definitive chemoradiotherapy, Brown *et al.* (22) recommended introducing ART at week 3 for NPC. From a parotid protection point of view, replanning in the fourth week seems appropriate since parotid shrinkage occurs in a linear pattern initially and reaches its peak at the 16th fractions as shown by Ren *et al.* (28). A study by Gai *et al.* (23) showed that 85% NPC patients had ≥50% of GTV shrinkage before the 21st fractions and parotid volume decreased significantly in the first 4 weeks, thereby suggesting replanning between the 21st to 25th fractions. It appears that the most common time-frame for ART is between 30–50 Gy (i.e., the 15th–25th fractions) during a course of 33–35 fractions (17,29).

Since ART currently remains a labor-intensive effort and not all NPC patients would significantly benefit, proactive identification of patients who might benefit using pretreatment clinical characteristics remains a research focus. Advanced NPC with bulky primaries or nodal disease seem to be a candidate subset for proactive ART. Brown *et al.* (30) found that higher N-category, larger pre-treatment largest involved lymph node (LN) size, and

greater initial body weight (BW) were predictors for ART. They classified NPC patients into 3 risk groups for ART: low-risk: LN <6 cm with BW <100 kg or LN <1.5 cm with BW >100 kg; intermediate risk: N2-N3 disease or LN > 6.0 cm with BW >100 kg; high-risk: N2-N3 disease, or BW >100 kg or LN >1.5 cm with BW >100 kg. The study by Zhao *et al.* (4) showed that patients with a T3-T4 primary or N2-N3 neck disease had an improved 3-year LRC with ART compared to case-matched control patients. A single-arm phase II study (JCOG1015, UMIN000005448) of two-step IMRT (ART at 46 Gy) for 75 stage II-IVB NPC patients showed excellent overall survival (3-year: 88%) with an acceptable toxicity profile. However, 13 patients (17%) experienced locoregional failure, which seems unexpectedly high compared to other contemporary series; this raises the question whether volume-based adaption based on the second CT scan is safe. Yu *et al.* (26) studied pre-treatment MRI of 70 NPC patients and identified several pre-treatment MRI-based radiomic features (2 shape, 3 texture and 1 first-order features) from the GTV that suggested promising capability of identifying a subset of NPC patients who may benefit from ART. However, whether these features are a surrogate for GTV or truly independent additional features remains to be validated.

Challenges and opportunities for ART

Several challenges exist in implementing ART in routine clinical practice, including accuracy in image registration and dose accumulation, resource-demanding image acquisition, labor-intensive and time-consuming recontouring and replanning, and streamlining optimal ART workflow.

Accuracy in image registration is pivotal for assessing dose accumulation. Since any subsequent CT scan would have a different clinical target volume and normal tissue volume shapes, deformable image registration (DIR) is often preferred over rigid registration to obtain a better estimation of accumulated dose (31). However, registration errors could still exist in DIR, especially for structures that are small with lack of contrast with the background (e.g., air spaces, such as nasal cavity and paranasal sinuses), which could result in significant dosimetric deviation relating to target volumes and OARs, especially in spinal cord and optic apparatus in some NPC patients (32). The accuracy of DIR also depends on the DIR methods and interface area (33). Currently, several DIR algorithms are under investigation, which use different transformation frameworks, DIR registration algorithms, and mapping direction (34).

Currently, ART requires reimaging, recontouring and replanning using a diagnostic quality scan (e.g., planning CT). Since NPC patients often require daily volumetric imaging for setup verification, which could provide another potential source for dose calculation. However, the quality of verification volumetric images is still suboptimal and subject to noise and artifacts which could results in errors and uncertainties for deformable registration (35,36). In addition, the field of view of verification imaging is often narrow and unable to capture the anatomical information of all LNs in NPC patients, which also a limitation of using them for ART (37).

One of the most labor-intensive and time-consuming steps in ART is manually contouring the target volumes and OARs (38). Auto-contouring software has the potential to enhance the efficiency of ART and reduce the variation among radiation oncologists (39,40). Several vendors are developing auto-segmentation software for clinical use of ART; however, they are not available yet for routine clinical use in NPC due to the complexity of the anatomy of this location of the head and neck region and minimal tissue density difference for satisfactory auto-segmentation. Studies by Fung *et al.* (38) showed that auto contouring OARs could reduce the total replanning time by more than 30%, and the geometrical discrepancies between the auto- and manual contours were insignificant when compared to inter-observer variations. However, the dosimetric impacts of such contour differences could still be substantial in some NPC patients. This suggests the need for manual review and edit of auto-contours in a real clinical setting, which may not always be a time-saving measure compared to traditional approaches. Studies have shown that atlas-based auto-segmentation for OARs and neck volumes are feasible, but human intervention and quality assurance is also required (41-44).

Conclusions

NPC patients remain a vulnerable group from the standpoint of anatomical changes during a 6–7-week course of IMRT. ART shows promising potential to reduce toxicities while enhancing LRC. However, ART is currently still at an early stage of development in terms of precise method, workflow, and clinical implementation. ART is yet to be implemented routinely in clinical practice for all NPC patients since it is a time consuming and labor-intensive process. Timing and thresholds to trigger reactive

ART remain active research areas. ART is most frequently implemented between 15–25 fractions over a course of 6–7 weeks radiotherapy to take into account potential significant anatomical changes and also allow sufficient time to adapt. Computer-assisted auto-contouring seems promising to address the labor-intensive aspect of ART; however, it is still at its nascent stage of development and further refinement is warranted. Caution must be taken when performing DIR and dose accumulation for cases with significant volume changes (45-47). Rigorous quality assurance should be implemented to assess the accuracy of auto-contouring for OARs and target volumes. Technical advances, such as machine learning and artificial intelligence to refine deformable registration, dose accumulation, and auto-contouring algorithms, may pave the way for adopting pragmatic approaches in implementing ART routinely for NPC patients; this could further improve their oncologic and functional outcomes.

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