

Adaptive radiotherapy for bladder cancer – a systematic review

KONG, Vickie, TAYLOR, Amy <<http://orcid.org/0000-0002-7720-6651>> and ROSEWALL, Tara

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1 **Adaptive Radiotherapy for Bladder Cancer – A Systematic Review**

2 Keywords: Bladder cancer; adaptive radiotherapy

3 **ABSTRACT**

4 Radiotherapy has been offered as a multi-modality treatment for bladder cancer patients.
5 Due to the significant variation of bladder volume observed throughout the course of
6 treatment, large margins in the range of 20 – 30 mm have been used, unnecessarily
7 irradiating a large volume of normal tissue. With the capability of visualizing soft tissue
8 in Cone Beam Computerized Tomography, there is opportunity to modify or to adapt the
9 plan based on the variation observed during the course of treatment for quality
10 improvement. A literature search was conducted in May 2016, with the aim of examining
11 the adaptive strategies that have been developed for bladder cancer and assessing the
12 efficacy in improving treatment quality. Among the 18 identified publications, three
13 adaptive strategies were reported: Plan of the Day, patient-specific planning target
14 volume and daily reoptimization. Overall, any of the adaptive strategies achieved a
15 significant improvement in reducing the irradiated volume compared to the non-adaptive
16 approach, outweighing the additional resource required for its execution. The amount
17 and the type of resource required vary from strategy to strategy, suggesting the need for
18 the individual institution to assess feasibility based on the existing infrastructure in order
19 to identify the most appropriate strategy for implementation.

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22 **List of Abbreviation**

23 CBCT: Conebeam CT

24 CTV: Clinical Target Volume

25 DIR: Deformable Image Registration

26 IMRT: Intensity Modulated Radiation Therapy

27 OAR: Organ at Risk

28 PLN: Pelvis Lymph Node

29 POD: Plan of the Day

30 PS-PTV: Patient-specific PTV

31 PTV: Planning Target Volume

32 ReOpt: Daily ReOptimization

33 VMAT: Volumetric Modulated Arc Therapy

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40 INTRODUCTION

41 The typical clinical target volume (CTV) for bladder radiotherapy consists of the pelvic
42 lymph nodes (PLN), the entire bladder and the primary tumor ¹. High precision
43 radiotherapy such as 3 dimensional conformal or intensity-modulated radiotherapy
44 (IMRT) techniques have been recommended to optimize the dose to the target and the
45 adjacent organs at risk (OAR) ². However, substantial internal motion of the bladder
46 during the treatment course necessitates the use of population-based Planning Target
47 Volume (PTV) margins in the range of 20 – 30 mm ^{1,3,4}.

48 Image guidance using Cone Beam Computed Tomography (CBCT) has improved target
49 localization via soft tissue visualization and has reduced setup errors ⁵. Despite these
50 improvements in treatment precision, there are barriers to reducing the PTV margin for
51 bladder loco-regional radiation therapy. The radiation fields must include two
52 independent moving targets: the PLN, which are relatively immobile, and the highly
53 distensible bladder, which can vary in volume and position.

54 In the presence of two independent moving targets, adaptive radiotherapy has been
55 demonstrated to be the best strategy in the treatment of PLN and prostate when
56 compared to various translational correction strategies ^{6,7}. Adaptive radiotherapy is
57 defined as “a closed-loop radiation treatment process where the treatment plan can be
58 modified” by measuring an individual’s target and OAR geometric variations ⁸. Due to
59 the large interfraction and interpatient variation observed for bladder cancer, various
60 | adaptive strategies have been specifically developed. [A literature review was conducted](#)

61 | ~~with T~~the purpose of ~~this paper is to d~~describe each of these adaptive strategies, and
62 | to compare/contrast their potential to improve treatment quality.

63 | **METHODS AND MATERIALS**

64 | A literature search was performed in May 2016 using the PubMed and the Google
65 | Scholar databases. ~~U~~Using the combination of the following keywords, ~~to identify~~ all
66 | English language peer-reviewed articles that reported on the development and efficacy
67 | of bladder cancer adaptive radiotherapy strategies using CBCT were identified: Bladder,
68 | adaptive radiotherapy, online, offline and CBCT. Only articles that were published after
69 | 2006 were included, when CBCT was widely introduced for clinical application. The
70 | reference sections of identified articles were also individually searched to include
71 | publications that were not indexed in the PubMed database. Reasons for exclusion
72 | are~~were~~: Evaluation of CBCT; use of imaging modality other than CBCT; validation of
73 | algorithm; description of clinical trial and related training; overview on dose
74 | accumulation; accuracy on volume delineation; assessment of intrafraction motion;
75 | general overview of Genitourinary/bladder radiotherapy, literature review on bladder
76 | adaptive radiotherapy. The PRISMA flow chart of the literature review is displayed in
77 | Figure 1.

78 | After reviewing the publications, each was categorized as one of the following adaptive
79 | strategies: Plan of the Day (POD), Patient-specific PTV (PS-PTV) and daily
80 | reoptimization (ReOpt). Details of the various studies were then extracted and
81 | organized to develop a detailed description of individual strategy, contrasting the
82 | strategy with the other approaches and highlighting its pros and cons.

83

84 **FINDINGS**

85 A total of 18 published studies that investigated various adaptive strategies for bladder
86 radiotherapy are included in this review and are summarized in Table 1.

87 *Plan of the Day (POD)*

88 Based on the large and random variation in bladder volume observed during treatment,
89 it is hypothesized that the single distribution generated based on an expansion on the
90 planning bladder would lead to either a geographical miss of the target or over-
91 irradiation of normal tissue. In order to resolve this, a POD library consisting of multiple
92 distributions generated based on PTV of various sizes was proposed. Different
93 approaches in generating the POD library are discussed below but generally, CBCT are
94 acquired prior to daily treatment delivery, and the smallest PTV that can encompass the
95 target volume on that day is selected. The corresponding POD distribution is then used
96 to deliver the dose of the day. Burridge et al. (2006) were the first to report the use of
97 CBCT for selecting the POD based on the bladder size prior to daily treatment ⁹. This
98 strategy has subsequently been investigated by various groups to assess its efficacy in
99 OAR sparing and target coverage ¹⁰⁻²³.

100 There are various methods of constructing the different sized PTVs for the POD library,
101 which could be based on a single image or multiple images. For single-image based, a
102 standard PTV is first generated by expanding the bladder by a population margin in the
103 range of 15 – 30 mm. A library of 3-6 PTVs is then created by applying an isotropic
104 margin in increments of 5mm to the bladder ¹⁴, or by changing the margin in the

105 superior and/or anterior directions in which bladder exhibits greater variation ^{9,11,17}. In
106 the study by Vestergaard et al. (2010), various isotropic margins that would provide
107 coverage for 50%, 70%, and 90% of the population were applied to generate the POD
108 library ¹⁰. Although this method is simple, the use of a single image in generating the
109 POD library lacks the ability to characterize individual's bladder filling and irregular
110 deformation pattern, diminishing its ability to fully compensate for volume variations.

111 The use of anatomical information from multiple planning images enables the
112 generation of a POD library that is more patient-specific and is able to account for the
113 significant inter-patient variability in bladder variation observed in this group of patients.
114 Lalondrelle et al. (2011) first reported the generation of a POD library using bladder
115 delineated on multiple successive CTs acquired at different time intervals, starting with
116 an empty bladder ¹². This strategy has been investigated by a few other groups ^{11,17,19}.
117 In general, the irradiated volume was reduced when compared to using a population-
118 based static PTV approach. However, depending on the filling rate and the length of
119 time in which the successive CTs were acquired, target under-dosage was observed in
120 >20% of cases, demonstrating the inadequacy of this approach in capturing the whole
121 range of bladder volume ^{11,12,17}. Instead of scanning an empty bladder first, Meijer et al.
122 (2012) acquired the first CT with a full bladder and acquired the second one after the
123 patient had voided ¹⁶. Six different PTVs were then generated based on information
124 provided from these two scans. This increased the target coverage to 100% and
125 achieved the same goal of reducing the irradiated volume based on qualitative
126 evaluation. Although multiple CTs were acquired, some argue that this was still
127 insufficient to capture the full spectrum of anatomical deformation of bladder observed

128 through the course of treatment, nor does it address systematic differences between
129 bladder volumes at planning and treatment^{20,22,24}.

130 The inclusion of CBCTs acquired at the beginning of the treatment course when
131 generating the POD library was proposed and investigated^{10,12,13,15,18,21,22}. In this
132 approach, bladder was delineated on the planning CT and first 4-5 CBCTs. The POD
133 library was generated based on different combinations and/or numbers of volumes. For
134 example, in Vestergaard et al. (2010), the smallest PTV was derived based on the
135 combination of the 2 smallest volumes, medium based on all combined volumes and
136 large by expanding a population margin on the bladder on CT¹⁰. When comparing the
137 POD library generated based on multiple CTs vs. combination of CT and CBCTs, a
138 larger irradiated volume resulted from the former method. However, the inclusion of
139 CBCTs achieved better target coverage with a smaller irradiated volume²². Images
140 acquired on multiple days captured the volume variation for bladder and the positional
141 variation based on changes in rectal filling³. Furthermore, less time is required at the
142 time of planning to acquire multiple CTs.

143 Although the POD strategy has been demonstrated as effective at improving plan
144 dosimetry when compared with a non-adaptive approach, there are some
145 acknowledged challenges with this adaptive strategy. Depending on the number of
146 PTVs available and how they are generated, the planning resource burden could be
147 heavy. Acquisition of multiple CT scans exposes patients to additional dose and adds
148 procedural time to both the patient and the department. Resources invested to construct
149 the POD library and the associated multiple treatment plans is considered wasted when
150 some of the PTVs are not used or are selected in low frequency. For example, 6

151 different distributions were generated for the 6 PTVs in the POD library reported in
152 Murthy et al. (2011). However, only 3 out of the 6 PTVs were eventually selected for
153 treatment ¹⁴.

154 *Patient-Specific PTV (PS-PTV)*

155 Similar to the multiple image POD strategy, information from the CT and CBCTs can be
156 incorporated to derive a single patient-specific PTV (PS-PTV). A PS-PTV can be
157 generated by creating a structure by combining the volumes of bladder delineated on
158 the planning CT and the first few CBCTs, then adding a small expansion margin to
159 incorporate additional uncertainties. Instead of selecting different distributions based on
160 the bladder of the day (POD strategy), a single distribution is generated based on the
161 PS-PTV and is used to deliver the remaining course of treatment ^{17,25-27}. This approach
162 is therefore more logistically viable than the multiple plan POD approach. Moreover, all
163 studies reported a significant decrease in the irradiated volume when compared to a
164 standard PTV. It is important to note that the target coverage ~~rate~~ was reported to be
165 >95% when the PS-PTV was derived based on a full bladder and inclusion of 5 CBCTs
166 ^{25,26}, whereas ~~it the rate~~ decreased to 50% when it was derived based on an empty
167 bladder and inclusion of 3 CBCTs ¹⁷. A disadvantage of the PS-PTV strategy is that
168 changes observed during the beginning of the treatment course cannot be corrected
169 immediately due to the need of information gathering from the first few treatments. In
170 addition, if the bladder is significantly smaller in subsequent fractions compared to the
171 first 4-5 fractions, the efficacy of PS-PTV in OAR sparing could be reduced. Conversely,
172 a larger bladder volume in the later part of treatment could result in geographical miss of
173 the target. Therefore, despite significant dosimetric and logistical advantages, the

174 efficacy of the PS-PTV approach is reliant on the bladder volumes from the first few
175 fractions being representative of the bladder filling variation throughout the remainder of
176 the treatment course.

177 *Daily Re-optimization (ReOpt)*

178 Since there are large and random variations in bladder volume and shape from fraction
179 to fraction, it is hypothesized that daily re-optimization (ReOpt) would be the best
180 strategy to achieve optimal target coverage and OAR sparing. This can be achieved by
181 acquiring daily CBCT and performing online modification of the plan prior to treatment
182 delivery based on the anatomy visualized on the CBCT ²⁸ and has been demonstrated
183 to be feasible for palliative and pelvic radiotherapy, with acceptable dosimetric accuracy
184 and timeframe ^{29,30}. Vestergaard et al. (2013) performed a comparison between a
185 standard PTV and the POD and ReOpt strategies for bladder radiotherapy ¹⁸. The
186 reduction of the irradiated volume achieved by ReOpt was significantly greater than
187 POD. For a total prescription of 60Gy, ReOpt reduced the volume receiving ≤ 45 Gy by
188 58% whereas POD reduced it by 20% compared to a standard PTV ¹⁸. However, the
189 requirement to delineate the bladder while the patient is on the couch and the
190 generation of a new distribution for every fraction can be resource intensive. The cost-
191 benefit of adopting this strategy has yet to be critically assessed to determine the
192 feasibility of implementing it clinically and its impact on departmental resources.

193 **DISCUSSION**

194 This comprehensive and systematic literature review identified three major adaptive
195 strategies for the treatment of bladder cancer described and/or evaluated in 18 studies:

196 POD, PS-PTV and ReOpt. Each strategy has been demonstrated as effective at
197 reducing the irradiated volume when compared to a non-adaptive approach but with
198 considerable variation in the magnitude of that effect. A number of factors can have an
199 impact on the efficacy of these strategies: Bladder status at the time of planning and
200 treatment, accuracy and precision of bladder delineation on CT and/or CBCT, and
201 reproducibility in image assessment.

202 Some institutions adopt the empty bladder protocol for better bladder volume
203 reproducibility, improved patient comfort and reduction of irradiated volume ^{9-13,15,17-22,27}
204 whereas others prefer the use of full bladder preparation for improved sparing of normal
205 tissue ^{16,23,25,26}. Webster et al. (2013), reported poor target coverage using the PS-PTV
206 strategy and an empty bladder protocol ¹⁷, whereas those studies that evaluated PS-
207 PTV in combination with a full bladder protocol report excellent target coverage
208 statistics ²⁵. It may therefore be suggested that full bladder is more efficacious if a PS-
209 PTV strategy is to be employed, especially when there is difficulty achieving an empty
210 bladder towards the end of treatment due to swelling and incomplete emptying due to
211 toxicity. To date, there is no direct comparison of the impact of full or empty bladder on
212 the efficacy of the other two adaptive strategies.

213 Bladder delineation is a critical task in the adaptive process and variability among
214 observers and between CT and CBCT is unavoidable. The single image based POD
215 strategy could be less affected by delineation variability since the PTVs are generated
216 using a single bladder contour delineated on the highest quality image (planning CT)
217 resulting in small delineation variability ³¹. For the multiple image based POD, the PS-
218 PTV and the ReOpt strategies however, the PTVs are derived based on the multiple

219 bladder contours delineated on often poor quality image datasets (CBCT) and are thus
220 susceptible to a higher degree of observer variability ³². Auto-segmentation tools will
221 have an important role to play in the improvement of both efficiency and precision of
222 bladder adaptive strategies that require multiple bladder contours delineated on poor
223 quality images ^{33,34}.

224 Excellence in CBCT assessment is necessary to accurately distinguish the bladder from
225 the adjacent normal tissue when selecting the appropriate PTV for treatment using the
226 POD strategy. Prior to the implementation of the POD strategy, Foroudi et al. provided a
227 training workshop and that educational intervention was deemed to be effective in
228 improving the quality of POD-based treatment delivery by reducing the plan selection
229 variability ³⁵. Similarly, very high skill levels are required for the soft-tissue CBCT
230 matching necessary for the PS-PTV, particularly when the PTV is highly irregular or
231 when complex 3D surface-based matching surrogates are required. The clinical
232 application of ReOpt will require the greatest level of skill in CBCT image assessment.
233 Where treating radiation therapists may be required to recontour and replan on-the-fly
234 while the patient is on the couch, there is opportunity for scope expansion in which high-
235 level clinical skills in image interpretation and delineation of treatment volume are to be
236 developed and applied.

237 There are a number of limitations in the findings of the various studies reviewed. The
238 majority of the studies considered only the reduction of the geometric PTV volume as
239 the benefit of using adaptive radiotherapy without reporting the actual dose to the target
240 and/or OARs ^{9,12,13,15-17,19,25,26}. The benefits postulated are predicated on the
241 assumption that the volume receiving the prescribed dose and the defined target

242 volume is a perfect overlap. However, despite the use of highly conformal techniques
243 such as IMRT and VMAT, perfect conformity is rarely clinically achievable. This can
244 result in an over or under estimation of the differences between the adaptive strategies.
245 For studies that included a dosimetric comparison, the dosimetric differences were
246 calculated without accounting for any OAR anatomical changes exhibited during
247 treatment ^{10,11,23,27}. This is problematic since the OARs adjacent to the bladder dome
248 can be in a different location from fraction to fraction. With this lack of accounting for the
249 dosimetric effect of OAR positional changes, it is clear that no study to date can
250 accurately predict the dosimetric differences between any of these adaptive strategies.
251 Deformable image registration (DIR) has been previously used to account for the
252 significant changes in volume and shape of the bladder and the adjacent OARs
253 between the planning CT and CBCTs ³⁶. Certainly, the application of DIR techniques to
254 accurately discriminate between bladder adaptive strategies is urgently necessary.

255 **CONCLUSION**

256 Three adaptive strategies ³⁶ have been developed for bladder cancer radiotherapy to
257 address the large interpatient and interfraction bladder volume variation observed. All
258 strategies have demonstrated significant improvement in reducing the irradiated volume
259 without compromising target coverage, yet definitive dosimetric evaluations that
260 incorporate the effect of OAR motion are currently lacking. In lieu of compelling
261 dosimetric evidence, individual institutions should adopt the strategy that best fits their
262 clinical processes and existing infrastructure based on the strengths and limitations of
263 each strategy.

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