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Adaptive radiotherapy for bladder cancer – a systematic review

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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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INTRODUCTION

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

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

In the presence of two independent moving targets, adaptive radiotherapy has been demonstrated to be the best strategy in the treatment of PLN and prostate when compared to various translational correction strategies [6,7]. Adaptive radiotherapy is defined as "a closed-loop radiation treatment process where the treatment plan can be modified" by measuring an individual's target and OAR geometric variations [8]. Due to the large interfraction and interpatient variation observed for bladder cancer, various adaptive strategies have been specifically developed. A literature review was conducted

61 with Tthe purpose of this paper is to ddescribinge each of these adaptive strategies, and

62 to compare/contrast their potential to improve treatment quality.

METHODS AND MATERIALS

64 A literature search was performed in May 2016 using the PubMed and the Google

65 Scholar databases. uUsing 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 arewere: 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 GenitourinaryU/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

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 CT [10]. 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 volume [22]. Images

140 acquired on multiple days captured the volume variation for bladder and the positional

141 variation based on changes in rectal filling [3]. 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 ≤45Gy 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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