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## Spatial descriptions of radiotherapy dose: normal tissue complication models and statistical associations

Martin Andrew Ebert, Sarah Gulliford, Oscar Acosta, Renaud de Crevoisier, Todd McNutt, Wilma D Heemsbergen, Marnix G Witte, Giuseppe Palma, Tiziana Rancati, Claudio Fiorino

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**PHYSICS IN MEDICINE AND BIOLOGY****TOPICAL REVIEW****Spatial descriptions of radiotherapy dose: Normal tissue complication models and statistical associations**

- Martin A Ebert<sup>1,2,3</sup>
- Sarah Gulliford<sup>4,5</sup>
- Oscar Acosta<sup>6</sup>
- Renaud de Crevoisier<sup>6a</sup>
- Todd McNutt<sup>7</sup>
- Wilma D Heemsbergen<sup>8</sup>
- Marnix Witte<sup>9</sup>
- Giuseppe Palma<sup>10</sup>
- Tiziana Rancati<sup>11</sup>
- Claudio Fiorino<sup>12</sup>

<sup>1</sup> School of Physics, Mathematics and Computing, University of Western Australia, Crawley, Western Australia

<sup>2</sup> Department of Radiation Oncology, Sir Charles Gairdner Hospital, Nedlands, Western Australia

<sup>3</sup> 5D Clinics, Claremont, Western Australia

<sup>4</sup> Department of Radiotherapy Physics, University College Hospitals London, United Kingdom

<sup>5</sup> Department of Medical Physics and Bioengineering, University College London, United Kingdom

<sup>6</sup> Univ Rennes, CLCC Eugène Marquis, INSERM, LTSI - UMR 1099, F-35000 Rennes, France

<sup>7</sup> Johns Hopkins University, Baltimore, Maryland, USA

<sup>8</sup> Department of Radiotherapy, Erasmus MC Cancer Institute, the Netherlands

<sup>9</sup> The Netherlands Cancer Institute, Amsterdam, The Netherlands

<sup>10</sup> Institute of Biostructures and Bioimaging, National Research Council, Napoli, Italy

<sup>11</sup> Prostate Cancer Program, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

<sup>12</sup> Medical Physics, San Raffaele Scientific Institute, Milano, Italy

Corresponding author:

Dr Martin A Ebert

1  
2  
3 Radiation Oncology  
4

5  
6 Sir Charles Gairdner Hospital  
7

8 Hospital Ave  
9

10  
11 Nedlands, Western Australia 6009  
12

13  
14 Australia  
15

16  
17 Tel: +61 423 976 746  
18

19  
20 Email: [Martin.Ebert@health.wa.gov.au](mailto:Martin.Ebert@health.wa.gov.au)  
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## 1 **Abstract**

2 For decades, dose-volume information for segmented anatomy has provided the essential data for  
3 correlating radiotherapy dosimetry with treatment-induced complications. Dose-volume information  
4 has formed the basis for modelling those associations via normal tissue complication (NTCP) models  
5 and for driving treatment planning. Limitations to this approach have been identified. Many studies  
6 have emerged demonstrating that the incorporation of information describing the spatial nature of  
7 the dose distribution, and potentially its correlation with anatomy, can provide more robust  
8 associations with toxicity and seed more general NTCP models. Such approaches are culminating in  
9 the application of computationally intensive processes such as machine learning and the application  
10 of neural networks. The opportunities these approaches have for individualising treatment,  
11 predicting toxicity and expanding the solution space for radiation therapy are substantial and have  
12 clearly widespread and disruptive potential. Impediments to reaching that potential include issues  
13 associated with data collection, model generalisation and validation.

14 This review examines the role of spatial models of complication and summarises relevant published  
15 studies. Sources of data for these studies, appropriate statistical methodology frameworks for  
16 processing spatial dose information and extracting relevant features are described. Spatial  
17 complication modelling is consolidated as a pathway to guiding future developments towards  
18 effective, complication-free radiotherapy treatment.

19 **Keywords:** radiotherapy, complications, modelling, dosimetry

20 **Word count:** ~15,500 (~22,000 with bibliography)

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## 1 Introduction

In radiotherapy, the risk of treatment-induced toxicity is the limiting factor for dose escalation in pursuit of an increase in local control. The prediction of radio-induced side-effects guides the physician and the patient between treatment alternatives and enables treatment optimisation by integrating predictive models within computerised planning.

Radio-induced toxicity is classically linked to the dose-volume relationship, patient clinical parameters (such as medical history and adjuvant treatments) and intrinsic radiosensitivity. With steady increases in computational capabilities and increased efforts to gather and analyse relevant data (Deasy *et al.*, 2010), exploiting information from more available data with integrative approaches is now feasible.

The dose-volume toxicity relationship has been widely investigated. In 2010, the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) review summarized the three-dimensional dose/volume/outcome data to update and refine the related normal tissue tolerance guidelines (Marks *et al.*, 2010), initially provided by Emami *et al.* (1991). Dose-volume histogram (DVH) based normal tissue complication probability (NTCP) models attempt to condense the dose-volume information into a number that expresses the risk of a certain toxicity. Most NTCP models are phenomenological and have the advantage of being characterized by few parameters (typically  $\leq 3$ ). Different approaches have been historically developed to model NTCP, with the Lyman–Kutcher–Burman (LKB) model being one of the first and most commonly employed (Lyman, 1985). Even if prediction of toxicity and treatment plan evaluation with the NTCP-based models is still common practice, these kinds of models present limitations reducing their prediction capability. DVHs reduce the 3D (or even 4D) dose distribution within an organ to a unidimensional and discrete representation of the dose-volume relationship, inhibiting the ability of models to account for the actual underlying complexity.

Spatial NTCP models have sought to geometrically represent the 3D dose distribution. This allows information on the pattern as well as the amount of dose to be characterised. Recent spatial NTCP models have sought to geometrically represent the 3D dose distribution in a single coordinate system via a spatial normalisation for a joint analysis of dose at the lowest sampling scale (pixel and voxel levels, referred to from here as “pixel-wise” in 2D and “voxel-wise” in 3D) (e.g., (Marcello *et al.*, 2020a; Mylona *et al.*, 2020b; Palma *et al.*, 2020a; Jiang *et al.*, 2019; Palma *et al.*, 2019b)). These low spatial-scale methodologies have allowed the unravelling of the local dose-effect relationship across a population at each single voxel in a common coordinate system in different organs. Models

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3 54 can also be created by defining and analysing spatial features of the 3D dose distribution (e.g.  
4 55 Buettner *et al.* (2012b)) or abstractions such as the dose surface map (DSM) (e.g. Heemsbergen *et al.*  
5 56 (2020)). These spatial methods, and others described below, have been pursued to improve  
6 57 prediction and classification. Such models may also facilitate identification of the underlying  
7 58 aetiology of radio-induced injury and be used to improve patient-specific treatment planning. They  
8 59 are likely to reduce toxicity (Drean *et al.*, 2016b; Lafond *et al.*, 2020), and may one day inform or  
9 60 help validate *in silico* models of treatment toxicity (e.g. Cicchetti *et al.*, 2020)).

16 61 The goal of this review is to describe these recent spatial dose-effect investigations and NTCP  
17 62 models and provide some guidance around their development.

## 21 63 **2 Strategies for characterising dose distributions**

### 24 64 **2.1 Dose-volume approaches**

26 65 The concept of the dose-volume relationship of a defined region of interest became commonplace  
27 66 when both 3D dose computation and 3D segmentation (“contouring”) of regions became practical.  
28 67 The cumulative DVH synthesises the dose vs volume relationship as a function representing the  
29 68 percentage of volume that receives at least a certain dose.

#### 34 69 *2.1.1 The advantages of dose-volume approaches*

35 70 The primary advantage of the dose-volume approach is linked to the wealth of knowledge obtained  
36 71 through prior studies of radiation and the resounding clinical success of such approaches. Today’s  
37 72 radiation therapy is driven by dose-volume constraints based on the results of published studies and  
38 73 meta-analyses. So much so, that today’s dose distributions contain little information outside the  
39 74 bounds of these dose volume parameters, as they are controlled for in clinical practice.

45 75 Dose-volume metrics are easily understood and are based on the natural compartmentalisation of  
46 76 the body into organs. Reporting of them can be reduced to a table of numeric entries representing  
47 77 the quality of the complex 3D treatment plan. To even further simplify their presentations, software  
48 78 applications have reduced them to colour codes to indicate alerts when a plan may violate one of  
49 79 the treatment goals. In busy clinics, this facilitates rapid evaluation. Dose-volume metrics are also  
50 80 convenient when defining the goals for optimization in inverse treatment planning.

56 81 Radiobiological models have been developed to bridge the gap between the physical dose-based  
57 82 objectives to drive treatment planning and the clinical dose goals reflecting the toxicity risks. Those  
58 83 commonly studied, such as NTCP, tumour control probability (TCP) and the complication-free



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3 84 tumour control probability (P+) (Källman *et al.*, 1992), have typically been designed to operate on  
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5 85 DVH information.  
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### 8 86 2.1.2 *The disadvantages of dose-volume approaches*

9 87 Fundamentally the DVH assumes that every sub-volume of the region is of equal importance to the  
10 88 function of that tissue and is equally sensitive to radiation dose. Realistically, the segmented regions  
11 89 in radiotherapy are typically bulk anatomy and do not reflect the microstructure of anatomy that  
12 90 may be impacted by radiation. Therefore, the DVH may be too coarse of a feature to adequately  
13 91 model the impact radiation may have on the anatomy.  
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19 92 The assumption that each element of tissue is equally important to the NTCP function and equally  
20 93 sensitive to radiation dose is simply not true for many anatomical regions typically segmented in  
21 94 treatment planning. For example, the parotid glands consist of acinar cells producing saliva and a  
22 95 ductal region that carries the saliva to the oral cavity. Similarly, a kidney is made up of several cell  
23 96 types and structures. In other cases, such as the oesophagus and rectum, organ structure consists of  
24 97 a mucosal layer surrounded by muscle tissue. These structures may have different risks when the  
25 98 dose is high to the entire circumference of the structure versus when it has the same volume of dose  
26 99 oriented longitudinally along the structure. Understanding the true causal relationships between  
27 100 radiation dose and normal tissue dysfunction is limited with dose volume metrics that are naive to  
28 101 the detailed components of the anatomy.  
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36 102 The spinal cord has a complex spatial arrangement of functional sub-units (FSUs - compartments  
37 103 that accomplish part of an organ's function), and subsequently a complex inter-relationship with  
38 104 overall organ function. Precise pre-clinical experiments performed by Bijl *et al.* (2003) identified  
39 105 large variations in dose-volume based predictors of paralysis in rats when the spatial patterns of  
40 106 irradiation were changed. Conventionally, simple maximum cord dose has been used to predict  
41 107 subsequent complications (Kirkpatrick *et al.*, 2010). However, the inhomogeneity in irradiation now  
42 108 afforded with stereotactic spinal radiosurgery exceeds the predictive capability of dose-volume  
43 109 analysis (Medin and Boike, 2011). Similarly, models of lung complication had focused on their  
44 110 parallel-like nature and mean lung dose (MLD) had conventionally been used as a principal predictor.  
45 111 However, evidence for more localised dose-response in humans emerged nearly two decades ago  
46 112 (Seppenwoolde *et al.*, 2004), following extensive animal experiments (as well reviewed by Voshart *et*  
47 113 *al.* (2021)).  
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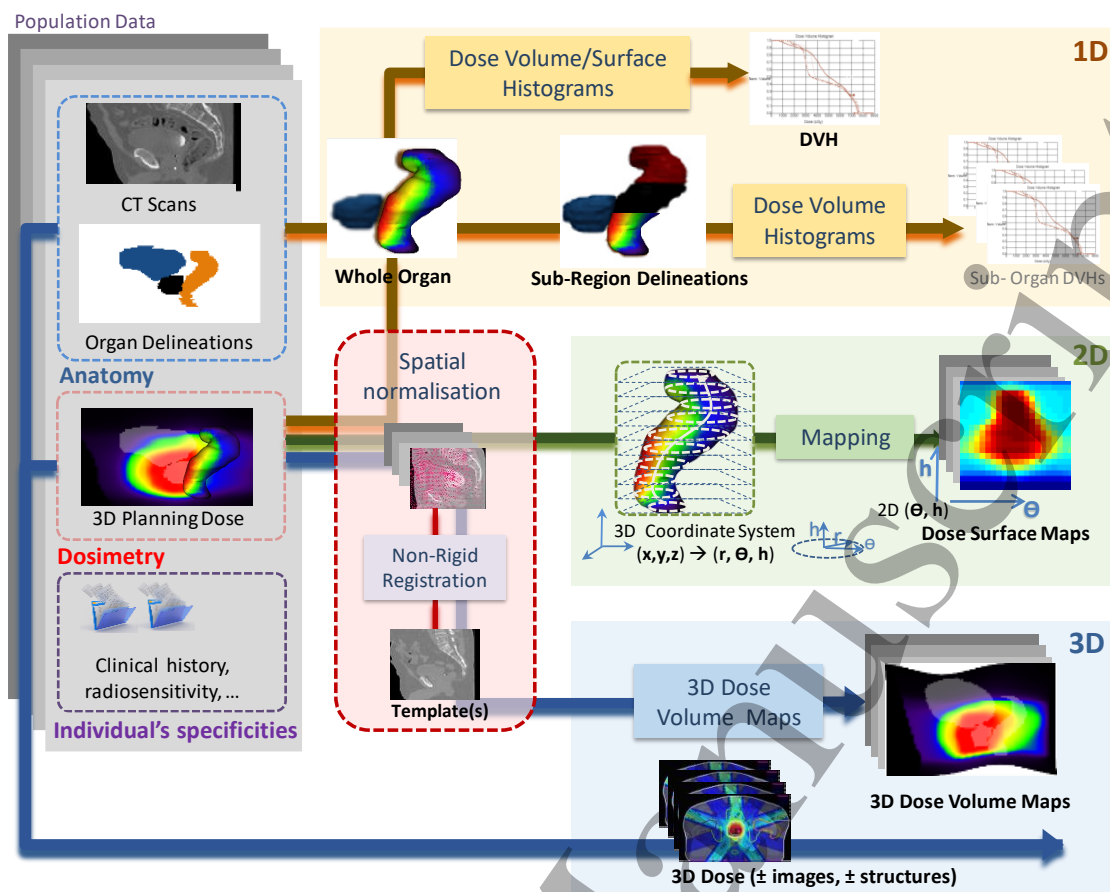
58 114 Further, analysis has traditionally been limited to dose-volume metrics for single organs. Many  
59 115 human functions involve multiple components of anatomy. Swallowing, for example involves many  
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3 116 muscles in the head and neck region. These muscles may be able to compensate for one another and  
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5 117 the impact of a dose pattern across the set of muscles and its impact on swallowing can be quite  
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7 118 complicated. In many cases, a significant portion of the anatomy is not contoured at all, and the  
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9 119 dose-volume metrics can only be computed for contoured regions. Contouring with high spatial  
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11 120 detail in routine workflow remains burdensome. Similarly, in a shift of spatial focus for dose-toxicity  
12  
13 121 association, the impact on lung toxicity from cardiac irradiation has been identified (Tucker *et al.*,  
14  
15 122 2014; van Luijk *et al.*, 2005).

16 123 Multiple spatial dose distributions (an essentially infinite number) will yield the same or similar DVH.  
17  
18 124 Dependence on a dose-volume approach requires an assumption that all those distributions will lead  
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20 125 to the same toxicity – the problem of *degeneracy*. Conversely, dose-volume derived NTCP models  
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22 126 from studies involving specific irradiation techniques will have been derived with minimal variation  
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24 127 in DVH between patients. Extrapolation of DVH and NTCP metrics beyond the specific context in  
25  
26 128 which they were derived is known to be dangerous. Due to this limitation, as well as many other  
27  
28 129 sources of variations between cohorts, DVH-based complication models derived for one treatment  
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30 130 approach tend not to be applicable to alternative irradiation strategies in the same sites (Troeller *et*  
31  
32 131 *al.*, 2015).

## 32 132 **2.2 Approaches that preserve spatial information**

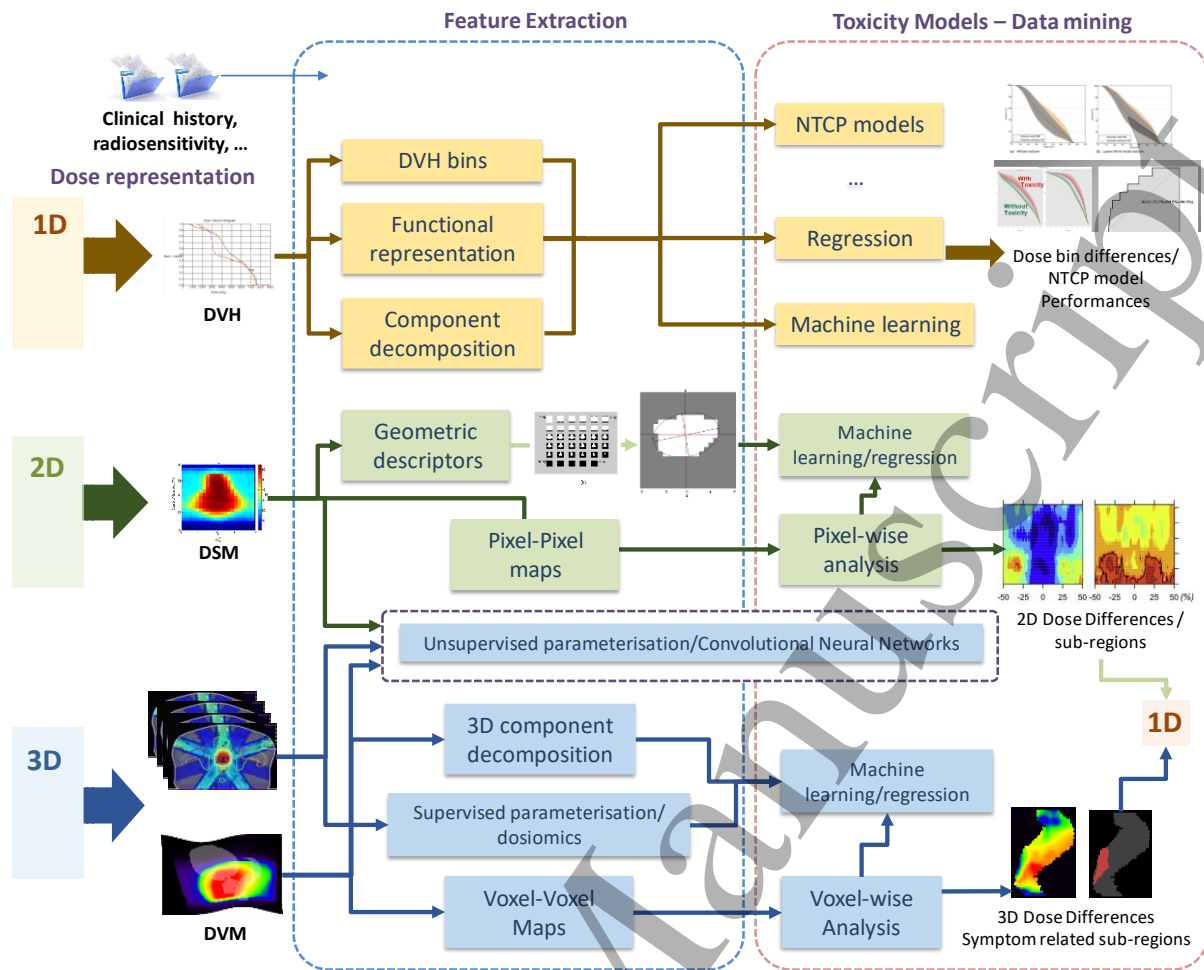
33 133 To overcome the limitation of whole organ DVHs, recent approaches have investigated the existence  
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35 134 of spatial signatures of dose distributions across dimensionalities and at diverse spatial scales. Here  
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37 135 we describe the processing of treatment planning data (Figure 1) required to achieve extraction of  
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39 136 features describing spatial distributions at the various spatial scales and development of subsequent  
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41 137 toxicity models (Figure 2). Practical applications of these features and models are described in  
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43 138 Section 5.



139

140 Figure 1. Processing workflows for preparing data for toxicity modelling across dimensionalities. Orange, path for  
 141 histogram development (1D data); green, path for 2D dose surface maps (2D data); and blue, path for 3D dose volume  
 142 maps (3D data). Some data sources and processes may not be used in all approaches, and these are indicated with  
 143 dashed borders.

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145 **Figure 2.** Data flow in the extraction of dosimetric features and construction of toxicity models. Features extracted from  
 146 1D, 2D or 3D data are exploited following different strategies, leading to different kinds of predictive models (NTCP,  
 147 machine learning or general regression). 2D DSM and 3D DVM models may require the entire population dose to be  
 148 mapped to a single coordinate system before being analysed.

### 149 2.2.1 1D precision dose-volume approaches

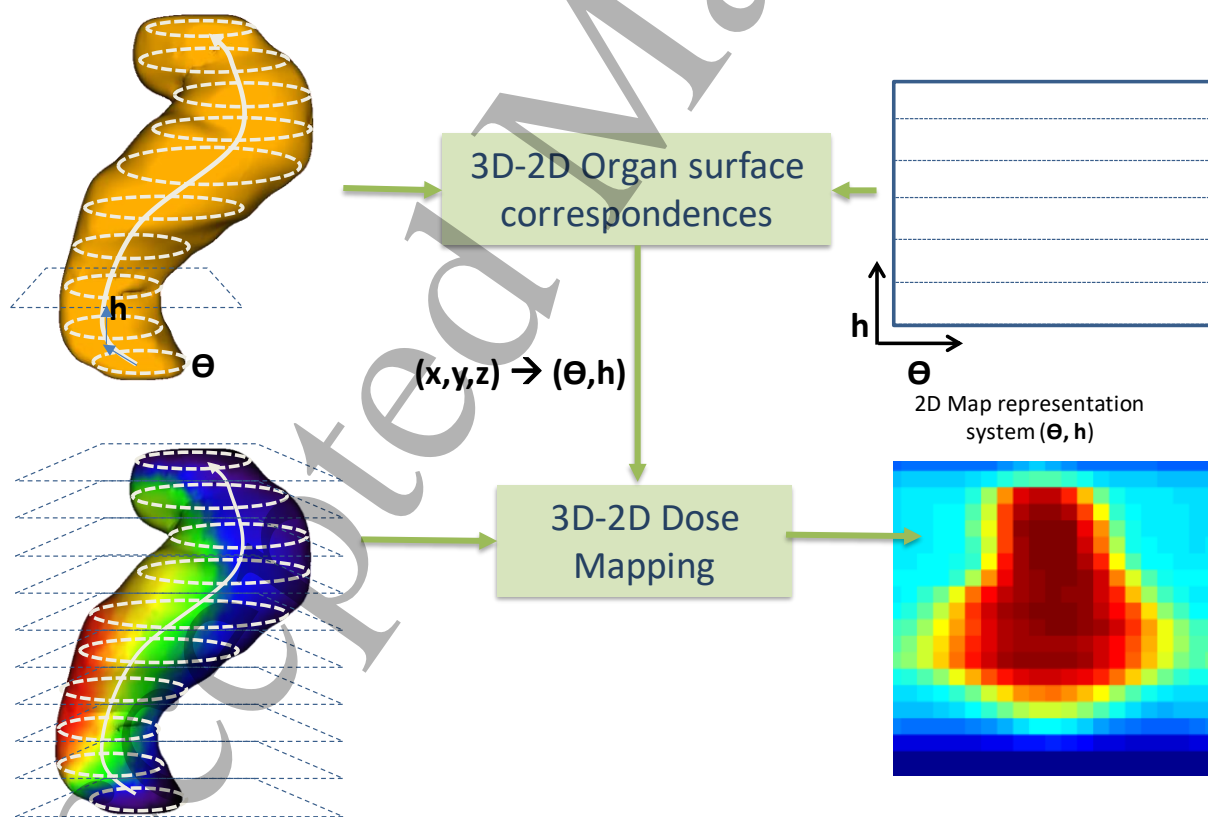
150 The simplest approach is to identify a more precise sub-region of the organ where dosimetry and  
 151 DVH metrics are most correlated with outcome. Improvements in NTCP models, and evidence of  
 152 correlations between local dose and side-effects, have been provided by undertaking DVH analysis  
 153 (or analysis with related histogram information) at spatial scales below the organ level. Partitioning  
 154 the organs for computing sub-region DVHs for example has demonstrated a sub-anatomical  
 155 dependence for specific toxicities (Ebert *et al.*, 2015b; Heemsbergen *et al.*, 2005; Peeters *et al.*,  
 156 2006b; Stenmark *et al.*, 2014). The question that may arise is whether the organ partitions are  
 157 anatomically-equivalent across individuals allowing DVH comparisons. If sub-region partitions  
 158 between patients are generated following the same geometrical criteria, then they can refer to the  
 159 same anatomico-physiological regions. The identification of correlative regions can be derived

60

160 manually (e.g. Gulliford *et al.* (2017)), or by identifying clusters of correlated pixels and voxels in 2D  
 161 and 3D representations (e.g. Drean *et al.* (2016b)). DVH-based features of those sub-regions can be  
 162 used to validate their association with complications.

### 163 2.2.2 2D surface mapping

164 Spatial considerations on the distribution of dose to an organ surface can be achieved with dose  
 165 surface mapping (DSM). DSMs present a virtual unfolded planar representation of the dose  
 166 distribution across an organ wall. Such mapping has been implemented following different strategies  
 167 (Sanchez-Nieto *et al.*, 2001; Hoogeman *et al.*, 2004; Munbodh *et al.*, 2008; Tucker *et al.*, 2006b;  
 168 Witztum *et al.*, 2016). A 2D image is constructed via parametric mapping from the 3D coordinate  
 169 system of the organ wall. The general idea is depicted with a rectal DSM in Figure 3, where a direct  
 170 relationship exists between the 3D cylindrical coordinates and the 2D  $(\theta, h)$  space. Thus, each pixel in  
 171 2D corresponds to a portion of the organ wall where the dose is mapped and propagated by  
 172 interpolation. Once constructed, dose surface maps can be used to undertake “pixel-wise” analysis  
 173 (Yahya *et al.*, 2017), or parameterised using geometric descriptors such as lateral and longitudinal  
 174 extent (Buettner *et al.*, 2009b) or texture features (Chen *et al.*, 2018).



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176 Figure 3: Construction of a dose surface map (DSM) for the rectum by establishment of a direct relationship between the  
 177 3D coordinate system and a planar  $O(\theta, h)$  space.

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3 178 Crucial aspects in this construction are the definition of the origin (i.e. 0,0) and the resolution and  
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5 179 size of the 2D images. If the rectum was the organ to be studied (e.g. (Buettner *et al.*, 2009a;  
6  
7 180 Moulton *et al.*, 2017)) a cylindrical coordinate system for building the DSM has been used. In  
8  
9 181 Buettner *et al.* (2009b) the contour was thus cut at the posterior-most position on each CT-slice and  
10  
11 182 unwrapped to a map of 21x21 pixels. Witzum *et al.* (2016) raised some of the issues concerning  
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13 183 tortuous structures. They developed a raytracing approach to create dose surface maps for the  
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15 184 duodenum accounting for the bend in the structure, following an inner path.

16  
17 185 In other hollow organs such as the bladder a similar slice-based methodology has been applied. In  
18  
19 186 works from Palorini *et al.* (2016a) and Yahya *et al.* (2017), 1 mm-resolution DSMs were generated  
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21 187 (cranial-caudal direction), by virtually cutting bladder contours at the points intersecting the sagittal  
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23 188 plane passing through its centre-of-mass. Because of the large inter-individual bladder variability  
24  
25 189 some issues arise when having large and small bladders to map together for population analysis or  
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27 190 where some parts of the bladder are not equally mapped. In Mylona *et al.* (2020a) this was  
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29 191 addressed with an anisotropic vertical interpolation to the smallest bladder, aligned at the bladder  
30  
31 192 base.

### 32 193 2.2.3 3D feature extraction

33  
34 194 It is feasible to reduce the complex 3D voxel-level dose information to a smaller number of features  
35  
36 195 via an appropriate spatial parameterisation. One such approach is to describe the spatial distribution  
37  
38 196 within an organ via 3D moments (Buettner *et al.*, 2012b; Dean *et al.*, 2016). Alternatively, borrowing  
39  
40 197 from the world of imaging analytics, supervised descriptions can be obtained via spatial texture  
41  
42 198 features (“dosiomics” (Liang *et al.*, 2019; Rossi *et al.*, 2018), “dosomics” (Placidi *et al.*, 2020) or  
43  
44 199 “radiomorphology” (Jiang *et al.*, 2019)), or unsupervised learning can be employed via neural  
45  
46 200 networks.

### 47 201 2.2.4 3D volume mapping

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49 202 At a fine scale, dose-outcome correlations can be investigated at the voxel level. For voxel-wise  
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51 203 comparisons to be meaningful, anatomical correspondence across the individuals must be ensured.  
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53 204 This pre-processing step is referred to as “spatial normalisation”, whose goal is to define geometrical  
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55 205 transformations aimed at registering and resampling inter-individual anatomies and doses into a  
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57 206 common coordinate system as depicted in Figure 1 (e.g. (Monti *et al.*, 2020; Acosta *et al.*, 2013;  
58  
59 207 Rigaud *et al.*, 2019; Acosta and De Crevoisier, 2019)). This 3D-3D dose mapping to a common  
60  
208 coordinate system to create a dose-volume map (DVM) remains challenging. Such mapping may be  
209  
210 209 obtained via a parametric representation of the anatomy in a spherical or cylindrical coordinate

210 system as in Chen *et al.* (2013). It may be more precisely computed through existing non-rigid  
211 (deformable) registration methods (McWilliam *et al.*, 2017; Monti *et al.*, 2018; Marcello *et al.*,  
212 2020a), or tailored to a particular anatomy as proposed for the rectum in Drean *et al.* (2016a), or for  
213 the bladder in Mylona *et al.* (2019) using spatial descriptors. Depending on the investigated  
214 anatomical site, organ-driven registration methods may be more precise than the ones based on  
215 intensity levels. This is the case in Acosta *et al.* (2013), Drean *et al.* (2016a) and Mylona *et al.* (2019)  
216 where anatomical mapping based on 3D structural models of the considered organs were proposed.  
217 These approaches require, nevertheless, a precedent segmentation of some of the considered  
218 structures such as the urethra (Acosta *et al.*, 2017). However, when inter-individual registration is to  
219 new patients without identified structures or is to be structure-agnostic, image information alone  
220 must be used (McWilliam *et al.*, 2017; Monti *et al.*, 2018; Abravan *et al.*, 2020).

221 The 3D spatial normalisation approach can also be used to align anatomy for derivation of DSMs,  
222 especially in the case of pixel-wise analysis, or for the purpose of sub-region identification.

### 223 **3 Practical Considerations**

224 The development of spatial response models places specific demands on the nature of technical data  
225 collected for their construction. When interpreting, utilising or publishing a spatial complication  
226 model, factors impacting the underlying technical data should be considered and appropriately  
227 reported and accommodated (see section 4.2.3). The relevance and quality of patient outcome data  
228 is of similar or even greater importance for the derivation of useful models. Additional data types  
229 can constitute modifying and stratifying co-variables, such as patient demographics and co-  
230 morbidities, disease staging, treatment characteristics (techniques, timing, adjuvant treatments),  
231 pathologic and genetic information.

#### 232 **3.1 Required technical data**

233 Due to the computational nature of spatial models, it is assumed that required data will be available  
234 in digital form which could be arbitrary in-house, native or proprietary formats, or more generally in  
235 prescribed formats such as Digital Imaging and Communications in Medicine (DICOM) (NEMA),  
236 Neuroimaging Informatics Technology Initiative (NiftI) (NiftI, 2020) or Nearly Raw Raster Data  
237 (NRRD) (SourceForge, 2020). The three principal technical data ingredients for model development  
238 are briefly described below.

##### 239 **3.1.1 Imaging**

240 Anatomical imaging typically provides the reference space for derived models, guides definition of  
241 segmented structures and facilitates intra- and inter-individual registration. The robustness of spatial  
242 models can depend significantly on the sensitivity and specificity of imaging, particularly through  
243 influence on the definition of structures (e.g. (Roach *et al.*, 2019)).

### 244 3.1.2 Structures

245 Many of the processes for characterising spatial dose distributions presented in Sections 2.2 and 5  
246 operate on information related to anatomical and functional structures. The definition of such  
247 structures can be made manually by observers at the time of patient treatment planning or manually  
248 through retrospective review of collated data. Alternatively, autosegmentation routines utilising  
249 anatomical atlases (Kennedy *et al.*, 2019) or artificial intelligence approaches (Fu *et al.*, 2020) can be  
250 used. Structure segmentation can represent a significant source of uncertainty in the derivation and  
251 application of models, with multiple contributing factors:

- 252 • Geometric variability: The location and extent of structures will depend on multiple factors  
253 relating to image quality, image sensitivity and specificity, inter-observer variability (e.g.  
254 (Roach *et al.*, 2019)), organ deformation and motion (e.g. (Palorini *et al.*, 2016a)), errors and  
255 limitations in image registration, bias propagated from atlas definitions or neural network  
256 learning environments or selection of a patient template (see Section 2.2) (Acosta *et al.*,  
257 2010).
- 258 • Structure definition: A common source of undesired variability, particularly when pooling  
259 data sources or during validation, is variable definition of anatomical structures (e.g.  
260 (Nitsche *et al.*, 2017)). Models need to operate on like-definitions. Variability and ambiguity  
261 can be reduced through the use of consensus definitions, reviews of definitions such as  
262 within the QUANTEC reports (Bentzen *et al.*, 2010), or published standards (Wright *et al.*,  
263 2019).
- 264 • Structure naming: Structure naming can often be problematic for scripting model  
265 development, particularly when data comes from multiple institutions. This can be  
266 ameliorated through use of naming conventions (e.g. (Mayo *et al.*, 2018; Santanam *et al.*,  
267 2012)) or ontologies (Phillips *et al.*, 2020). Note that spatial models may utilise or give rise to  
268 non-standard structures (such as predictive clusters identified in DSMs and DVMs).

### 269 3.1.3 Dose



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3 270 As indicated in Figure 1 and Figure 2, access to multi-dimensional descriptions of dose distributions,  
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5 271 or features derived from them, represents a common minimum level of required technical data.  
6  
7 272 When deriving and applying spatial models, several aspects of these data should be considered:

- 8  
9 273
- 10 274 • Accuracy: Although dose distributions are frequently available based on planned or intended  
11 274 treatments, correct models will be based on dose distributions which have been verified or  
12 275 accumulated as delivered (e.g. (Shelley *et al.*, 2017; Jaffray *et al.*, 2010)). Accuracy should  
13 275 ideally have been assessed independently, such as via participation in credentialing exercises  
14 276 (e.g., (Ebert *et al.*, 2011; Molineu *et al.*, 2013; Weber *et al.*, 2014)). Deformations of dose,  
15 276 due perhaps to the intra-individual accumulation process (Tilly *et al.*, 2013) or inter-  
16 277 individual co-registration (see Section 2.2.3) will impact on the accuracy of dose  
17 278 representation.  
18 278
  - 19 279 • Precision: Spatial resolution in the description of dose can impact the ability to precisely  
20 280 represent the underlying response effects. The resolution of dose calculation has previously  
21 280 been shown to impact even dose-volume based models (Ebert *et al.*, 2010; Kim *et al.*, 2018).  
22 281 Variation in resolution can have a moderate impact on dosimetric texture features (Placidi *et*  
23 281 *al.*, 2020). With an increasing need to develop models for precision stereotactic treatments,  
24 282 precise descriptions of steep dose gradients across spatially-limited structures are required  
25 283 (e.g. (Ryu *et al.*, 2007; Hrycushko *et al.*, 2019; Gale *et al.*, 2017; Kim *et al.*, 2014)).  
26 283  
27 284 • Completeness: Dose calculations are often limited in extent relative to potentially-involved  
28 284 anatomy, such as when based on cone beam CT data obtained with accelerator-mounted  
29 285 imaging systems. This can inhibit spatial models, particularly those relating to low-doses  
30 286 over extensive regions of anatomy.  
31 286  
32 287 • Temporal features: Dose fractionation, inter- and intra-fraction dose temporal patterns can  
33 287 impact complication incidence (Dörr, 2015). Changes in response due to variable dose-per-  
34 288 fraction, either between voxels or due to variable treatment phases, may need to be  
35 288 incorporated into the model. Such variations may also be accounted for using equieffective  
36 289 dose estimates (Bentzen *et al.*, 2012), noting that this leads to spatial discontinuities where  
37 289 parameters vary between tissues. The complexity of temporal dose effects increases  
38 290 significantly when intra-treatment variations due to organ motion or the pharmacokinetics  
39 291 of radionuclide deliveries are considered.  
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#### 56 300 3.1.4 Treatment description

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3 301 Treatment factors, such as patient set-up at imaging and treatment, patient preparation, the use of  
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5 302 immobilisation and fixation devices, may be co-variables of importance to the specificity of a model.  
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7 303 This information is often not captured in DICOM fields or through oncology information systems.  
8

### 9 304 **3.2 Outcome Data**

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11 305 Outcome information, providing the known output for a model (the “endpoint” or “event  
12  
13 306 incidence”), comes in diverse forms. For complication outcome, we are typically concerned with  
14  
15 307 organ-specific symptoms of radiation injury which may manifest over months or years. These can be  
16  
17 308 graded at discrete (ordinal) levels using standardised clinician- or patient-reported instruments such  
18  
19 309 as provided by the Common Terminology Criteria for Adverse Events (Trotti *et al.*, 2003) developed  
20  
21 310 by the United States (US) National Cancer Institute (NCI), instruments developed in-house or by  
22  
23 311 various international collaboratives. The trend is towards the use of patient-reported complications  
24  
25 312 for outcome. This is because the severity of symptoms are often under-reported by clinicians (Xiao  
26  
27 313 *et al.*, 2013), and follows recognition of the importance of focussing on symptoms with the most  
28  
29 314 impact on patients’ quality of life. Although definitions can vary, complications are typically graded  
30  
31 315 according to indicative symptoms and required interventions (GX – Grade X):

- 31 316 • G0 – symptoms are absent
- 32 317 • G1 – the complication is mild and no interventions are required
- 33 318 • G2 – the complication is moderate and some local intervention might be required
- 34 319 • G3 – the complication is severe and intervention is required, though is not life-threatening
- 35 320 • G4 – the complication is life-threatening and major intervention is required
- 36 321 • G5 – the complication has caused death

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42 322 Whilst some models can utilise continuous outcomes, for NTCP models it is common to convert  
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44 323 measures to a binary endpoint classification. These may be either determined at fixed time-points  
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46 324 following treatment, as incidence at any time during follow-up, or the time-to-event incidence if  
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48 325 temporal features can be incorporated in the model. The definition, interpretation, collection and  
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50 326 application of complication outcome measures are notorious sources of uncertainty in outcome  
51  
52 327 modelling. Multiple factors should be kept in mind related to model accuracy and generalisability:

- 53 328 • Specificity of the included patient cohort.
  - 54 329 • The relevance of an outcome to patient quality-of-life.
  - 55 330 • Variations in scoring mechanisms and criteria.
  - 56 331 • Variations in follow-up time or time between measurements.
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3 332           • The identification and influence of comorbidities, concurrent treatments or pre-existing  
4 333           morbidity.
- 5  
6 334           • The influence of social and/or technical factors on measures.
- 7  
8 335           • The nature of the data source, as discussed below.
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10

### 11 336 3.3 Data sources

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13 337 When considering sources of data for spatial complication models, we can consider the ability of  
14 338 those sources to meet specific criteria for development of generalizable, robust and powerful  
15 339 models. A source should provide large volumes of high quality, well-curated data for patients with  
16 340 diverse characteristics and treated with diverse techniques (noting that data diversity can lead to  
17 341 unexpectedly biased results, as discussed in Section 6.1). The sub-optimal performance of many  
18 342 radiotherapy outcomes models can largely be blamed on the paucity and lack of diversity of  
19 343 available data (Luo *et al.*, 2020).

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26 344 Table 1 lists specific criteria, provides some examples of sources and attempts to describe, via  
27 345 generalisations, how likely each source is to meet the criteria. In Table 1, *quality* infers the  
28 346 completeness, accuracy and consistency of technical and outcome data. *Diversity* relates to the  
29 347 variability in studied populations, radiotherapy technique and overall patient treatment, including  
30 348 trial vs non-trial contexts (Chen *et al.*, 2016; Krauss, 2018). Diversity also pertains to inter-individual  
31 349 variations in spatially-localised dose (note also the implications of diversity for model  
32 350 generalizability, as discussed in Section 6.2).

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39 351 Some points to note in relation to Table 1:

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41 352       - **Single-institution studies** enable ready access to appropriate high-quality data though with  
42 353       minimal variability and typically only small patient numbers. Collated data is rarely made  
43 354       available outside the institution.
- 44  
45  
46 355       - **Multi-centre clinical trials** often employ rigorous data collation. However, such trials will  
47 356       rarely be statistically powered specifically for the purpose of spatial response modelling and  
48 357       so the sample size may be insufficient. Software systems developed over the last couple of  
49 358       decades, both in-house and commercially, have facilitated quality assessment of technical  
50 359       data by multicentre trials groups (e.g. (Ebert *et al.*, 2010; Deasy *et al.*, 2003; La Macchia *et al.*,  
51 360       2012; Meroni *et al.*, 2019; Roelofs *et al.*, 2014; Deasy and Adita, 2013; Purdy, 2008;  
52 361       Purdy *et al.*, 1998)). Although the quality of clinical trial data can be advantageous, variations  
53 362       from trial conditions in the clinic, including participant selection, can bias model predictions  
54 363       relative to non-trial practice (Ohri *et al.*, 2013).

- 1  
2  
3 364 - **Data pooling and publication.** International policies are trending towards data availability  
4 and interoperability (e.g. (Hayman *et al.*, 2019; Taichman *et al.*, 2017)). In Table 1 we  
5 365 distinguish “public” pooling and publication, such as provided by the Cancer Imaging Archive  
6 366 ([www.cancerimagingarchive.net](http://www.cancerimagingarchive.net), (Clark *et al.*, 2013)), from “private” pooling, such as might  
7 367 be achieved via manufacturer-led knowledge base collaboratives and user-communities.  
8 368 Both public and private data pools have the potential for development of large cohorts with  
9 369 data variability, though data quality may be ambiguous if not well documented.  
10 370  
11 371 - **Federated data access** can enable accessing large patient cohorts spanning multiple  
12 372 repositories, including clinical systems at individual treatment centres. Ethical and socio-  
13 373 political issues can be minimised if model parameters can be estimated for data at each site,  
14 374 before being combined centrally (Deist *et al.*, 2017). Although no published evidence was  
15 375 found that spatial complication models have been derived through this approach, the  
16 376 potential for validation of developed models is significant.  
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28 378 **Table 1: Potential sources of data for spatial models and their ability to meet desirable criteria for forming**  
29 379 **statistically-powerful, generalisable models that meet current standards for validation and translation.**

Source	Technical data quality	Outcome data quality	Variability/ diversity	Sample size	FAIR	Facilitates validation
Single institution studies	High	High	Low	Low	Low	Low
Multicentre clinical trials	High	High	Medium	Medium	High	Medium
Public data pooling and publication	Variable	Variable	Medium	Medium	High	High
Private data pooling	Variable	Low	Medium	High	Medium	Variable
Federated data access	Low	Low	High	High	Variable	High

380 <sup>a</sup> Including dosimetric accuracy.

381 <sup>b</sup> A data source will have a high ability to satisfy this criterion if it meets the FAIR principles  
382 (Wilkinson *et al.*, 2016) defined by the FORCE 11 (Future of Research Communications and e-  
383 Scholarship) community, of data being findable, accessible, interoperable and re-usable.

384 <sup>c</sup> e.g., Treatment planning system manufacturer-facilitated knowledge base consortia.

## 385 4 Statistical and Modelling Considerations

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386 A central aim of using spatial dose descriptors to model dose-complication is to reduce the impact of  
387 degeneracy relative to dose-volume approaches. It is important that the process utilised maintains  
388 the principles associated with robust, unambiguous statistical analysis and interpretation. Here we  
389 summarise such relevant considerations.

## 390 4.1 Feature Selection

### 391 4.1.1 Candidate dosimetric features and collinearity

392 An important step in developing phenomenological NTCP models (van der Schaaf *et al.*, 2015) is to  
393 start off with a list of potential prognostic factors based on the literature and underlying  
394 radiobiological assumptions (e.g. assumed  $\alpha/\beta$  ratio). This can reduce the number of false positive  
395 findings and guide the feature reduction process (Palma *et al.*, 2020a; Heinze *et al.*, 2018). The  
396 inhomogeneous physical dose distribution can be aggregated into dose features (Figure 2) that  
397 represent the biological dose received and are predictive for the toxicity endpoint of interest. The  
398 result may be just a small number of features as derived from a spatial parameterisation. However,  
399 hundreds to thousands of dose features can be retrieved from a spatial voxel-wise 3D dose  
400 distribution, even though the sample size may be quite limited, and collinearity is likely. Candidate  
401 prognostic factors selected from a group of correlated variables are typically those that have the  
402 highest predictive power at univariate analysis compared to the correlated variables that are a priori  
403 excluded. A general rule of thumb is that correlation between candidate variables for a multivariable  
404 model should be below  $\approx 0.7$  (El Naqa *et al.*, 2009; Schaake *et al.*, 2016).

### 405 4.1.2 Feature reduction

406 The generally accepted rule of thumb is that regression models should be used with a minimum of  
407 10 "events per variable" EPV (Peduzzi *et al.*, 1996). This rule has been criticized as being too strict -  
408 Vittinghoff and McCulloch (2007) instead recommend a minimum of 7 EPV. After pre-processing the  
409 dataset to a candidate list of features considered for modelling, a variable selection algorithm must  
410 be chosen (Heinze *et al.*, 2018; Steyerberg and Vergouwe, 2014). Valid approaches to reduce the  
411 number of features (and clinical co-variates) to the most predictive in a multivariate model are: 1)  
412 select variables for the final multivariable model based on their univariate model estimates, using a  
413 p value threshold; 2) backward and forward selection tools like Wald, Likelihood Ratio and  
414 conditional regression methods; and 3) the LASSO method (least absolute shrinkage and selection  
415 operator) which is a logistic regression analysis with a penalty for the magnitude of the regression  
416 coefficients to prevent overfitting (Tibshirani, 1996; Buettner *et al.*, 2011; Gabryś *et al.*, 2018).  
417 Consideration can be given to reduction of features through use of their principal components

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3 418 (e.g.(Chen *et al.*, 2011)). Additionally, feature selection can be combined with the method to  
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5 419 determine association with outcome through algorithms such as random forest, and through the  
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7 420 stability of features in associative models derived from sampled sub-sets of the full data (i.e.  
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9 421 “bootstrapping”). Adequate feature reduction is vital to ensuring the ability for a model to be  
10  
11 422 generalised. An excellent overview of techniques is provided in Guyon and Elisseeff (2003).

#### 12 13 423 *4.1.3 Co-variates*

14 424 The inclusion of clinical factors in NTCP models may improve the predictive power of the model  
15  
16 425 considerably (Defraene *et al.*, 2012; Morimoto *et al.*, 2019; Rancati *et al.*, 2011; Dean *et al.*, 2017;  
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18 426 Palma *et al.*, 2020b). A preselection of all treatment- patient- and tumour- related factors by an  
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20 427 educated guess is needed to avoid false positive results. For this purpose, a literature search is  
21  
22 428 recommended to define candidate clinical factors to be considered subsequently in model building  
23  
24 429 (Steyerberg and Vergouwe, 2014).

#### 25 26 430 *4.1.4 Models and Algorithms*

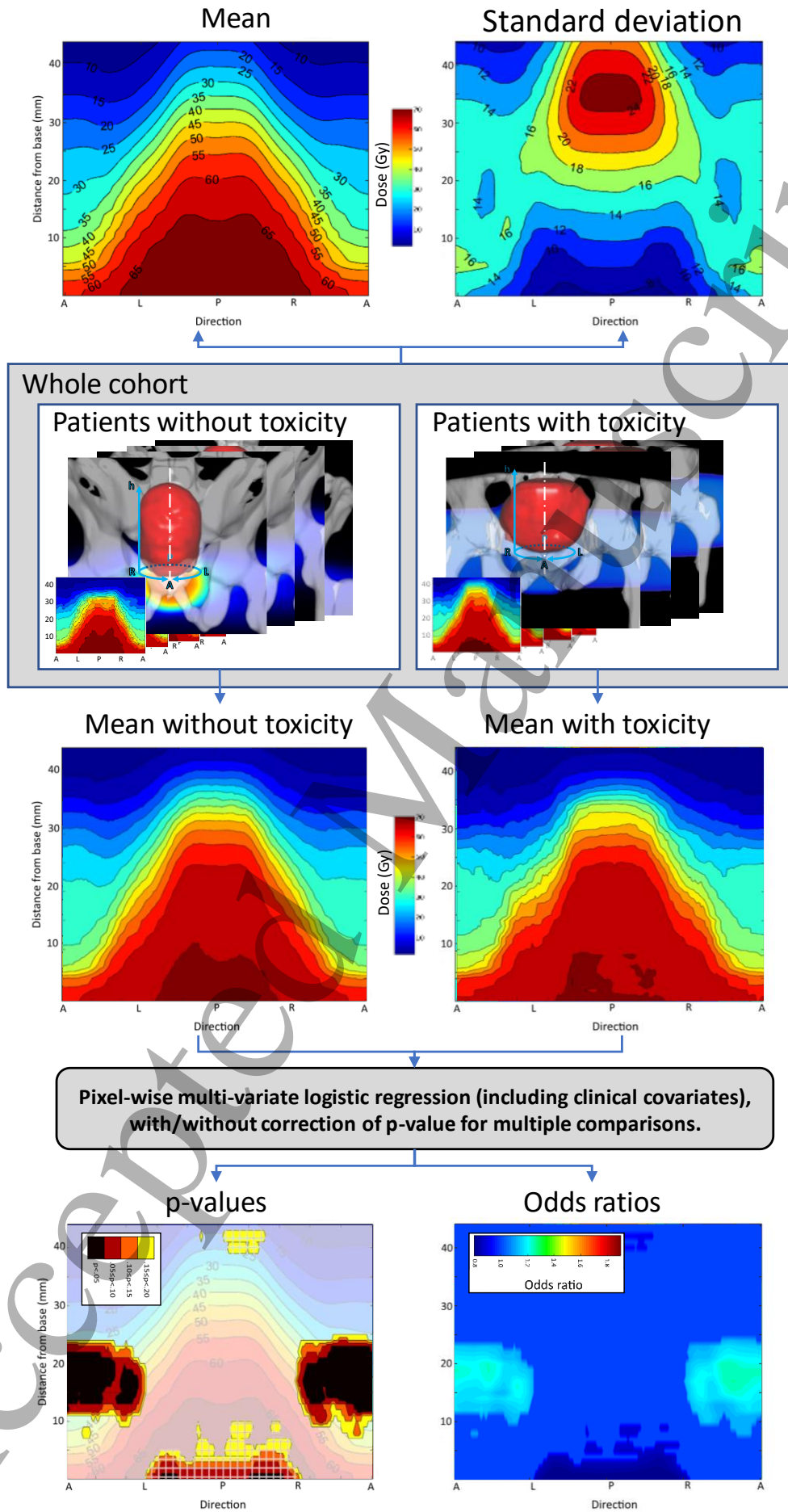
27 431 To parametrize the dose-dependence of an organ at risk, typically a sigmoid-shaped function is  
28  
29 432 fitted, like the LKB model, the Relative Seriality (RS) model, and the general logistic regression model  
30  
31 433 (Trott *et al.*, 2012). It has been demonstrated that the general applied logistic regression technique  
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33 434 produces very similar dose-effect curves as the LKB and RS model (Defraene *et al.*, 2012). A  
34  
35 435 prerequisite is that the type and pattern of toxicity (i.e. the dependent variable) has to be translated  
36  
37 436 and captured in a ‘present (1)/not present (0)’ for logistic regression modelling.

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39 437 As an alternative in the current information age, data mining and machine learning approaches for  
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41 438 toxicity prediction research are increasingly applied (Robertson *et al.*, 2015; Beasley *et al.*, 2018;  
42  
43 439 Gabryś *et al.*, 2018; Luo *et al.*, 2020; Dean *et al.*, 2018; Palma *et al.*, 2019a). Commonalities and  
44  
45 440 differences between the more conventional methods of model-based statistical inference and the  
46  
47 441 rapidly progressing field of data driven machine learning have given rise to an active debate (c.f. the  
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49 442 field of imaging in neuroscience (Bzdok, 2017)). It has been shown that machine learning approaches  
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51 443 do not, by default, result in better predictions (Yahya *et al.*, 2016; Dean *et al.*, 2018). Unsupervised  
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53 444 machine learning approaches aim to produce accurate predictions for unseen data based on a large  
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55 445 body of training data, and do not depend on tractable relations between variables, which can limit  
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57 446 sensible extrapolation of the associated models. Conventional regression, on the other hand, may  
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59 447 reveal the specific dependence of a given variable on several independent variables within a data  
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448 set. From this comes the opportunity to extrapolate beyond the initial model fitting, beyond the  
449 initial conditions under which data were acquired, by adaptation.

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3 450 Selection of the appropriate statistical test(s) depends on the nature of the predicted outcome. If  
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5 451 time to event is considered important, parameters of a proportional hazards model may be  
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7 452 inspected (provided proportionality of the hazard is valid), or e.g. accelerated failure time models  
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9 453 may be employed (Bradburn *et al.*, 2003). On the other hand, when fixed time point differences or  
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11 454 incidence over multiple time points are considered sufficiently descriptive, parametric t-tests or  
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13 455 nonparametric signed-rank tests can be performed (Lumley *et al.*, 2002). Rather than to seek  
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15 456 rejection of a null-hypothesis, Bayesian analysis may provide a more informative description of  
16  
17 457 observed differences (Kruschke, 2013).

#### 18 458 *4.1.5 Voxel-wise models*

19 459 Although conventional statistics can be applied at a pixel-wise or voxel-wise level, a comparison of  
20  
21 460 the aggregated data dichotomised by endpoint is a commonly used approach. Detailed descriptions  
22  
23 461 and formalisms of the process for voxel-wise analysis for toxicity studies are provided by Acosta and  
24  
25 462 De Crevoisier (2019) and Palma *et al.* (2020a). The idea of identifying local dose-response patterns  
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27 463 by voxel-wise analysis based on two-sample tests was derived from neuroimaging studies where the  
28  
29 464 aim is to discover voxel-wise changes due to a specific disease (Ashburner and Friston, 2000;  
30  
31 465 Whitwell, 2009). When comparing DSMS/DVMs, the null-hypothesis is that there is no difference  
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33 466 between the dose distributions of the patients with and without toxicity, which can be tested either  
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35 467 using parametric (e.g. Student's T-test) or nonparametric tests (e.g. the Mann-Whitney U test or the  
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37 468 Wilcoxon rank-sum test). In both cases, a map of p-values can be filled in voxel by voxel, pinpointing  
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60 469 where are the significant differences between the groups of patients.





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3 471 **Figure 4: Example of voxel (pixel)-wise assessment of a dose-complication relationship for a change in international**  
4 472 **prostate symptom score (IPSS) of  $\geq 10$  in a prostate radiotherapy trial cohort (Yahya *et al.*, 2017). Bladder DSMs have**  
5 473 **been derived by cylindrical mapping using 200 equally-spaced radial samples at each interpolated 1 mm slice vertically**  
6 474 **from the bladder base (up to 45 mm for all patients). Pixel-wise logistic regression incorporating clinical factors leads to**  
7 475 **the (uncorrected) p-value and odds ratio maps shown, including demonstration of a confounding protective effect of**  
8 476 **dose at the bladder base.**

11  
12 477 Logistic regression, LKB modelling or Logit dose-response modelling are possible alternative  
13 478 approaches to studying local dose-response effects at the voxel-level (as illustrated via an example  
14 479 for DSMs in Figure 4). For each voxel in the DSM/DVM, the relationship between the dose and the  
15 480 incidence of a selected toxicity endpoint is calculated. When the actuarial incidence of the side-  
16 481 effect is considered, Cox regression constitutes a suitable choice (Marcello *et al.*, 2020a; Marcello *et*  
17 482 *al.*, 2020b). This analysis produces a map of best-fit parameters, constant and b-coefficient for dose  
18 483 for the logistic regression, TD50 (uniform dose corresponding to 50% complication probability) and  
19 484 slope at TD50 for LKB and Logit models,  $H_0(t)$  and  $\beta$ -coefficient for dose when Cox is used. This kind  
20 485 of analysis allows identifying regions where the dose-response is steeper vs areas where it is  
21 486 shallow, thus providing a hypothesis for treatment optimization on selected sub-regions.

22  
23  
24 487 Clinical risk factors can be included, with the inclusion of multiple b-coefficients/  $\beta$ -coefficients in  
25 488 logistic and Cox regressions and with the addition of dose modifying factors in LKB and Logit models  
26 489 (Peeters *et al.*, 2006a). Of note, in this case, a map of effect sizes for the clinical risk factors is  
27 490 produced, with a variation of effect sizes at the voxel level. Discussion is still open on the meaning of  
28 491 these variations, with the possibility of a clinical factor to be a protective factor in some voxels and a  
29 492 risk factor in others. A possible alternative way to include clinical risk factors is to use local dose-  
30 493 based modelling to determine areas with different dose-response curves and apply an adjustment  
31 494 for clinical risk factors at a sub-region level or a patient level.

#### 32 495 *4.1.6 Significance*

33 496 From a modelling perspective a large variation over the population provides the best opportunity to  
34 497 derive a high-quality dose-effect model (see Table 1). Techniques that result in high rates of toxicity  
35 498 do not necessarily exhibit a large variation over patients. When deriving statistics at the voxel-level,  
36 499 dose deposited by external beams gives rise to correlations between dose variables. Establishing  
37 500 significance based on per-voxel null hypothesis testing (see Section 5.2) severely suffers from  
38 501 multiple testing issues – the likelihood of incorrect rejection of that hypothesis. Methods based on  
39 502 estimated false discovery rate (FDR) have been proposed, which have been shown to hold under  
40 503 positive dependencies (Benjamini and Hochberg, 1995; Benjamini and Yekutieli, 2001; Storey, 2002).  
41 504 Permutation methods can be used to establish significance based on test statistics aggregated over

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3 505 the individual voxels (Manly, 1997; Chen *et al.*, 2013; Palma *et al.*, 2020a): a pertinent global  
4 506 threshold of the single-voxel test statistic is derived, leading to the selection of voxels that exceed  
5 507 that value. Reporting the adjusted map beyond arbitrary thresholds for significance (such as the  
6 508 commonly-used  $p = 0.05$ ) might be suggested, allowing readers to make a more informed conclusion  
7 509 by also considering the trends and spatial patterns of association, rather than focusing on specific  
8 510 highly significant voxels (Palorini *et al.*, 2016b).

## 14 511 **4.2 Performance, validity and reporting**

15 512 Three main purposes of statistical models can be identified: 1) predictive/prognostic models,  
16 513 focussing on event prediction; 2) explanatory models explaining difference in outcome via  
17 514 explanatory variables, focussing on (causal) relationships and the magnitude of effects; and 3)  
18 515 descriptive models with the main purpose to capture accurately the association between the  
19 516 dependent variable and the independent variables, which may focus on both elements of  
20 517 prediction, relationships and magnitude of effects (Shmueli, 2010).

### 27 518 *4.2.1 Model performance*

28 519 NTCP models are descriptive models, describing the relationship between biological dose, clinical  
29 520 cofactors, and toxicity risks. To evaluate discriminative (predictive) power, the performance of the  
30 521 model is commonly reported through the area under the receiver operating characteristic curve  
31 522 (AUC) which is a measure that combines the specificity and sensitivity in one number (Dean *et al.*,  
32 523 2018; Men *et al.*, 2019). In case of a large imbalance in the data, the F-score based on precision-  
33 524 recall could additionally be considered (Saito and Rehmsmeier, 2015).

### 40 525 *4.2.2 Model validity*

41 526 The internal validity of a prediction model concerns the reproducibility of the underlying data. To  
42 527 avoid overfitting and unstable models, preferred methods for internal validation are cross-validation  
43 528 and bootstrap resampling techniques (Heinze *et al.*, 2018; Steyerberg and Vergouwe, 2014; Xu *et al.*,  
44 529 2012). For the external validation of the model, concerning the generalizability of the results to  
45 530 other similar patient populations outside the database and outside the institution, independent  
46 531 validation datasets are required (Bentzen *et al.*, 2010). A relevant example is provided by Mylona *et*  
47 532 *al.* (2020b), where dosimetry for sub-regions in the bladder was found to be more predictive of  
48 533 complications than that for the whole organ, as validated in an external cohort.

### 56 534 *4.2.3 Model reporting*

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3 535 It is recommended to report at least the following characteristics of a developed phenomenological  
4 536 (data-driven) NTCP model (Jackson *et al.*, 2010; Collins *et al.*, 2015): study population, received  
5 537 treatment, definition and measurement of predicted outcome, dose-volume information of full  
6 538 organs and relevant sub-volumes, basic statistical data on incidence of toxicity including number of  
7 539 subjects and number of events, complication rates associated with constraints, available follow-up  
8 540 time, statistical motivation of sample size, handling of missing data, numerical range and median of  
9 541 the dosimetric variables of interest, model parameter estimates and their standard errors, applied  
10 542 feature selection method (model building algorithm), candidate variable list, applied validation  
11 543 methods, goodness-of-fit and discriminative power of the final model. For spatial models, it is also  
12 544 recommended to report dose-grid resolution and dose calculation algorithm (Placidi *et al.*, 2020),  
13 545 and a definition for the algorithms used in extraction of features (e.g. (Zwanenburg *et al.*, 2020)). A  
14 546 checklist for transparent reporting is available through the TRIPOD initiative (Collins *et al.*, 2015).

## 25 547 **5 Review of methods – spatial dose associations with complications** 26 548 **and applications to NTCP calculation**

27 549 Section 2 defined, in general terms, approaches that may be used, in various dimensions, to  
28 550 represent dose information in ways that retain spatial information from which features may be  
29 551 extracted. Section 3 detailed where the data may be obtained from to inform those processes, and  
30 552 for describing the complication outcomes with which the features will be correlated, using the  
31 553 statistical processes described in Section 4. We can now review publications which attempt to  
32 554 combine these to derive NTCP models and for examining associations of spatial dose information  
33 555 with complication incidence.

34 556 Evidence of improved predictive capabilities with models which are inclusive of spatial information  
35 557 have been emerging from analysis of isolated data sets over the last 10 – 15 years. Table 2 provides  
36 558 a summary of some previously published analyses where a comparison has been made between  
37 559 histogram-based toxicity models and those incorporating various forms of spatial dose information.

560

561 **Table 2: A selection of published studies comparing histogram-based toxicity modelling to models incorporating spatial information. Note that some studies incorporated multiple**  
 562 **approaches to spatial feature extraction.**

Reference	Tumour site	Evaluated region	Toxicity endpoint	Spatial method	Comparison	Impact on complication prediction
Heemsbergen <i>et al.</i> (2005)	Prostate	Rectum	Various	Pixel-wise, DSM sub-regions	Total rectum DSH vs sub-regions alone	Several specific toxicities only associated with spatially-localised dose
Peeters <i>et al.</i> (2005)	Prostate	Rectum	Acute rectal $\geq$ G2	Dose-length parameters	Total rectum DVH and DSH vs addition of spatial features	Most significant DVH and dose-length parameter both improved final model
Peeters <i>et al.</i> (2006b)	Prostate	Anorectum	Various	DVHs for sub-regions (rectum, anus)	Total anorectum DVH vs sub-regions	Specific toxicities better predicted by sub-region dosimetry
Acosta <i>et al.</i> (2013)	Prostate	Rectum	Rectal bleeding	Voxel-wise dose, DVM	Rectum DVH vs voxel-wise	Rectal bleeding only correlates with identified local dose levels, not with total rectum DVH.
Drean <i>et al.</i> (2016b)	Prostate	Rectum	Rectal bleeding	Voxel-wise and manually identified sub-region	Rectum DVH vs different sub-regions	DVH-based inferior-anterior hemi rectum (voxel-wise identified sub-region) performed best.
Casares-Magaz <i>et al.</i> (2017)	Prostate	Rectum	Various	Pixel-wise DSM	Rectal DVH and DSH vs pixel-wise	For all endpoints DSM-based parameters showed better AUCs (mean 0.64) than the best DSH/DSH-based parameters (mean 0.61)
Rossi <i>et al.</i> (2018)	Prostate	Rectum	Rectal bleeding Faecal leakage	3D texture features	Rectal DVH vs addition of spatial features	Bleeding - AUC increased 0.68 to 0.72; leakage - AUC increased from 0.68 to 0.75
Buettner <i>et al.</i> (2009a)	Prostate	Rectum	Rectal bleeding	CNN on DSM	Rectal DSH vs addition of spatial features	AUC increased from 0.59 to 0.64
Buettner <i>et al.</i> (2011)	Prostate	Rectum	Various	Parameterised DSM	NTCP based on rectal vs addition of spatial features	AUC increased from 0.59 to 0.63 – 0.67
Zhen <i>et al.</i> (2017)	Cervix	Rectum	General toxicity	DSM texture features and CNN (with transfer learning)	Peak dose-indices vs texture features vs CNN	AUC 0.47-0.58 (dose-indices), 0.70 (texture features), 0.89 (CNN)
Wilkins <i>et al.</i> (2020)	Prostate	Anorectum	Various	Parameterised DSM; manual sub-regions	Rectal DVH vs sub-region DVH vs DSM	DSM-based parameters did not improve prediction compared to DVH-based parameters;

				(rectum, anal-canal)	features	sub-region dosimetry not identified as more predictive
Heemsbergen <i>et al.</i> (2010)	Prostate	Bladder	Urinary obstruction	DVM, voxel-wise (specific local dose points)	DSH-based total bladder vs addition of local point dose trigone	Both DVH point and local trigone dose point added to final model
Improta <i>et al.</i> (2016)	Prostate	Bladder	IPSS toxicity score	Pixel-wise DSM	Bladder DSH vs addition of spatial features	AUC increased from 0.58-0.71 to 0.66-0.77
Palorini <i>et al.</i> (2016b)	Prostate	Bladder	Acute urinary symptoms	Pixel-wise and parameterised DSM	Bladder DSH vs parameterised DSM	For all endpoints DSM-based parameters showed better AUCs than the best DSH-based parameters
Rossi <i>et al.</i> (2018)	Prostate	Bladder	Nocturia Incontinence	3D texture features	Bladder DVH vs addition of texture features	Nocturia - AUC increased from 0.63 to 0.67; Incontinence - AUC increased from 0.71 to 0.73
Mylona <i>et al.</i> (2019)	Prostate	Bladder, urethra	Acute and late urinary symptoms	Sub-regions derived from voxel-wise DVM analysis	Bladder DVH vs sub-regions DVHs	AUC improvements in both acute and late toxicity in several sub-regions including the urethra (AUCs $\geq 0.62$ )
Beasley <i>et al.</i> (2018)	H&N	Head region	Trismus	Voxel-wise DVM	Organ vs sub-region DVH	Identified voxel cluster most significant
Buettner <i>et al.</i> (2012b)	H&N	Salivary glands	Xerostomia	Parameterised 3D organ dose distribution	Mean dose vs 3D moments	AUC increased from $\sim 0.7$ to $> 0.8$
Gabryś <i>et al.</i> (2018)	H&N	Parotid glands	Xerostomia	Parameterised 3D dose	Mean dose and parotid DVH vs addition of multiple spatial features	AUC increased from $< 0.6$ to 0.68 – 0.78 for dose-gradient features
Men <i>et al.</i> (2019)	H&N	Glands	Xerostomia	3D dose CNN and CT images	Combinations of basic dose-volume metrics, clinical parameters, and CNN based on images, structures and dose	AUC increased from 0.56 for dose metrics alone to 0.84 with all CNN information
Monti <i>et al.</i> (2017)	H&N	Neck region	Dysphagia	Voxel-wise DVM	Sub-region mean dose and multi-organ DVH (Alterio <i>et al.</i> , 2017)	AUC confirmed between multi-organ vs voxel-wise analysis ( $\sim 0.8$ )
Dean <i>et al.</i> (2018)	H&N	Pharyngeal mucosa	Dysphagia	3D spatial parameterisation	Organ DVH vs spatial features	DVH features as predictive as spatial features (AUC $\sim 0.71$ -0.82) and maintained on external

						validation
Dean <i>et al.</i> (2016)	H&N	Approximated oral mucosa	Acute mucositis	3D moments	Organ DVH vs addition of spatial features	No improvement
Dean <i>et al.</i> (2017)	H&N	Oral cavity	Acute mucositis	Sub-region definition (mucosal surface)	Organ DVH vs sub-region	No improvement
Palma <i>et al.</i> (2016)	Thorax	Lung	Lung fibrosis	Voxel-wise DVM identified sub-regions	Whole-lung mean dose vs sub-region-based mean dose	AUC increased from 0.60 to 0.75
Palma <i>et al.</i> (2019a)	Thorax	Lung	Lung fibrosis	Voxel-wise DVM	LKB vs 3D model (PACE)	AUC increased from 0.66 to 0.85
Lee <i>et al.</i> (2020)	Lung	Oesophagus	Weight loss	3D texture features	Combinations of DVH and radiomic/dosiomic features	Substantial increases in AUC though addition of spatial features
Liang <i>et al.</i> (2020)	Lung	Lung	Pneumonitis	3D dose texture features and CNN	DVH vs NTCP vs dosiomics vs 3D CNN	AUC increased from 0.676 (DVH) to 0.744 (NTCP) to 0.782 (dosiomics) to 0.842 (CNN)

563

564 Figure 5 illustrates the progression from dose-volume to spatial models of varying complexity, using  
 565 the relationship of pelvic radiotherapy dose to gastrointestinal complications as an example.  
 566 References describing studies are provided, grouped according to the complexity of anatomical  
 567 information used and by the spatial dose features used in the investigations. Many of the cited  
 568 studies are discussed in more detail below.

		Anatomical information					
		2D	3D				
		2D rectum BEV	3D rectum	Manual sub-regions	Broader pelvic anatomy	Statistical sub-regions	Structure agnostic
Primary feature definitions	1D (Histograms)	Estimated DVH	Emami et al 1991				
		Calculated DVH		Fiorino et al 2002; Gulliford et al 2004; Rancati et al 2004; Sohn et al 2007; Michalski et al 2010; Tomatis et al 2012; Ospina et al 2014; Fargeas et al 2018	Peeters et al 2006b; Buettner et al 2012; Stenmark et al 2014; Ebert et al 2015b; Gulliford et al 2017; Wilkins et al 2020	Smeenk et al 2012; Shaake et al 2016	Drean et al 2016b; Mylona et al 2020b
		DSH/DWH/zDVH		Cheng and Das 1999; Meijer et al 1999; Fiorino et al 2003	Buettner et al 2012; Kim et al 2014; Ebert et al 2015b; Wilkins et al 2020		
	2D (Dose-surface maps)	2D pixel-wise		Wortel et al 2015; Onjukka et al 2019			
		Parameterised		Heemsbergen et al 2005; Munbodh et al 2008; Buettner et al 2009b; Buettner et al 2011; Moulton et al 2017; Shelley et al 2017; Vanneste et al 2018; Henderson et al 2018; Casares-Magaz et al 2017, 2019	Buettner et al 2012; Wilkins et al 2020		
		Cluster model		Tucker et al 2006b			
		Supervised		Casares-Magaz et al 2017; Chen et al 2018			
		Unsupervised		Buettner et al 2009a;			
	3D (Dose-volume maps)	3D voxel-wise		Acosta et al 2013; Fargeas et al 2013;			Drean et al 2013; Marcello 2020; Ospina et al 2013; Chen et al 2011;
		Parameterised					
		Supervised		Rossi et al 2018			
		Unsupervised		Zhen et al 2017			Coloigner et al 2015

569

570 Figure 5: Illustration of the variety and evolution of methods for incorporation of dosimetric features into dose-  
 571 complication association studies and NTCP models in the context of gastro-intestinal toxicity. References are provided as  
 572 examples for studies involving various combinations of anatomical information and dosimetric feature extraction and  
 573 are not exhaustive. Studies can be further broken down according to the model used for association with complication  
 574 (see e.g., Acosta and De Crevoisier (2019)). (BEV – beam’s eye view).

575 **5.1 Use of histogram-based features**

576 **5.1.1 Description**



1  
2  
3 577 The degeneracy of the spatial dose distribution into the associated DVH of a structure may be  
4  
5 578 moderated if the dose distribution can be correlated with more specific descriptions of the  
6  
7 579 underlying functional structures themselves. This can be achieved, for example, by breaking a given  
8  
9 580 structure down spatially into more precise or component sub-structures according to some  
10  
11 581 anatomical or statistical criterion (as described in Section 2.2.1). The DVH characteristics of each sub-  
12  
13 582 structure can be considered independently. Analysis of more specific structures can also reveal that  
14  
15 583 dose to the originally-hypothesised structure of interest may be less correlated with complication  
16  
17 584 than alternative adjacent structures. It is also possible to utilise additional spatial information  
18  
19 585 regarding the structure (such as medical imaging scans) to modify the basic DVH information being  
20  
21 586 used as input to a dose-volume based NTCP model.

### 21 587 5.1.2 Examples

22  
23 588 A first class of models is based on the assumption that the organs can be thought of as organized in  
24  
25 589 functional sub-units (FSUs). If the density of FSUs  $f(\vec{r})$  is not homogeneous throughout the  
26  
27 590 considered structure  $\Omega$ , a more informative version of the DVH would be weighted by the  
28  
29 591 corresponding  $f(\vec{r})$  yielding  $fDVH(D_0)$ , defined as:

$$31 \quad 592 \quad fDVH(D_0) = \frac{\int_{\Omega} f(\vec{r})H[D(\vec{r}) - D_0]d\vec{r}}{\int_{\Omega} f(\vec{r})d\vec{r}}$$

32  
33  
34  
35 593 where  $H(\cdot)$  is the Heaviside step function (Lu *et al.*, 1997). Though DVH-based NTCP models would  
36  
37 594 be better recast on fDVH, it has been recognized that the derivation of the detailed underlying  
38  
39 595 arrangement of FSUs in most anatomical sites still requires dedicated studies from techniques such  
40  
41 596 as functional imaging (e.g. (Arslan *et al.*, 2018; Lee and Park, 2020)).

42  
43 597 For lung, a low-cost variation on the fDVH concept is represented by the dose-mass histogram  
44  
45 598 (DMH), in which the mass density (easily estimated from the planning CT) is considered as a  
46  
47 599 surrogate of FSU density. As expected, the DMH results to be independent of breathing phase  
48  
49 600 (Nioutsikou *et al.*, 2005; Cella *et al.*, 2015). Interestingly, however, a study on the risk of  
50  
51 601 postoperative pulmonary complications among oesophageal cancer patients found no evidence of  
52  
53 602 significant benefits from the substitution of DVHs with DMHs within the NTCP model (Tucker *et al.*,  
54  
55 603 2006a).

56 604 Similarly, for hollow organs such as the rectum, the absence of FSUs within the wall content led to  
57  
58 605 the development of the dose-wall histogram (DWH). DWHs represent the DVH of the organ wall only  
59  
60 606 based on the segmented outer organ contour (Meijer *et al.*, 1999). The dose-surface histogram



607 (DSH) lies, instead, on the histogram of the dose delivered to a representative surface of the organ.  
608 Two main approaches have been proposed for the DSH computation: one based on the interpolation  
609 of the dose on the organ surface (Lu *et al.*, 1995), and one normalizing the DVH of the organ wall by  
610 the shell depth in the limit of vanishing thickness (Palma and Cella, 2019). There is often a strong  
611 correlation between the various histogram types (Fiorino *et al.*, 2003; Carillo *et al.*, 2012; Hoogeman  
612 *et al.*, 2005). An exception is when the irradiation technique delivers a dose gradient that is steep  
613 relative to the organ size, such as found by Kim *et al* for prostate cancer patients treated with  
614 stereotactic radiotherapy (Kim *et al.*, 2014).

615 A first hybrid approach for including a notion of spatial dose distribution within a histogram  
616 framework is the zDVH (Cheng and Das, 1999), which expresses the volume receiving a given dose at  
617 a given cranio-caudal position in the form of a 2D histogram.

618 An effective approach based on pathophysiological knowledge of the toxicity aetiology consists in  
619 splitting a heterogeneous district into component substructures to achieve better DVH-response  
620 predictions. This approach has been made for the anorectum (Peeters *et al.*, 2006b; Ebert *et al.*,  
621 2015a) and the bladder trigone (Ghadjar *et al.*, 2014; Henderson *et al.*, 2018). Outcome associations  
622 have also been undertaken over broader spatial ranges of anatomy than conventionally  
623 hypothesised. For rectal toxicity in pelvic radiotherapy for example, although the gastrointestinal  
624 tract is usually targeted for derivation of associations, alternative structures can provide stronger  
625 associations with specific toxicities. Smeenk *et al* showed that incontinence was more strongly  
626 associated to dose to the pelvic floor muscles (Smeenk *et al.*, 2012), whilst Gulliford *et al* discovered  
627 the importance of dose to the peri-rectal fat space for control-like symptoms (Gulliford *et al.*, 2017).

628 The emergence of voxel-wise toxicity analyses in radiation oncology has fostered a data-driven  
629 evolution of this approach. This is aimed at defining, on a statistical basis, the relevant anatomical  
630 substructures involved in the development of radiation induced morbidity and from which  
631 histogram-based features can be extracted. This approach is described in Sections 5.2 and 5.4.

## 632 **5.2 Voxel-wise assessment**

### 633 *5.2.1 Description*

634 In contrast to analyses based on known or hypothesised FSUs as in Section 5.1, the use of voxel-wise  
635 methods points to an “agnostic”/bottom-up approach. Once the DSMs/DVMs in a cohort are  
636 spatially registered to a common coordinate system (see Section 2.2 for relevant details) in a way  
637 that they can be compared voxel-wise, the regions which are significantly associated to the

particular (toxicity) outcome are identified by statistical inference. Different approaches can be used, as described in Section 4.1.5. In general, the final goal of voxel-wise analysis is to identify regions driving the clinical manifestation of radio-induced side effects, i.e. to find clusters of voxels where the dose is significantly different in patients with/without toxicity (see also Section 5.4). The resulting organ sub-regions do not consider any prior anatomical or functional division. They can provide information to make inferences on the differential radio-sensibility of some organs or the simultaneous implication of different structures on some radio-induced toxicities.

Voxel-wise assessment does not by default generate an NTCP model. DVHs in the regions that were highlighted as statistically associated with the selected outcome should be considered to derive NTCP models following a classical dose-response analysis. Alternatively, a total complication risk can be formed from aggregation of risks determined at the voxel level.

### 5.2.2 Examples

#### **2D dose-surface outcome mapping**

2D DSMs (Section 2.2.2) are usually generated from an anatomical structure and restricted to the surface of this structure. This choice produces results which can be easily translated into organ sub-regions to be spared. Historically, the first analyses of DSMs in the radiotherapy field were related to hollow organs whose geometry could be easily associated with a cylinder, such as the oesophagus (Chen *et al.*, 2013; Dankers *et al.*, 2017) and the rectum (Casares-Magaz *et al.*, 2019; Munbodh *et al.*, 2008; Onjukka *et al.*, 2019; Sanchez-Nieto *et al.*, 2001; Tucker *et al.*, 2006b; Wortel *et al.*, 2015). Although pixel-wise assessment can be made to derive patterns of response, significant progress has been made by parameterising the DSMs, reducing the number of features and providing parameters for NTCP models, as discussed in Section 5.3.

Pixel-wise studies have related DSMs for the bladder with a number of early and late urinary endpoints (Palorini *et al.*, 2016b; Mylona *et al.*, 2020a; Palorini *et al.*, 2016a; Yahya *et al.*, 2017; Improta *et al.*, 2016). Recently a method for the calculation of DSM for the heart was implemented by using a modified cylindrical coordinate system (McWilliam *et al.*, 2020). DSMs of the heart were analysed to infer possible local dose effect for survival after lung cancer radiotherapy. The rationale for considering heart DSMs rather than DVMs resides in the location on the surface of some clinically relevant sub-regions, such as the coronary arteries, the electrical conduction system and the myocardium.

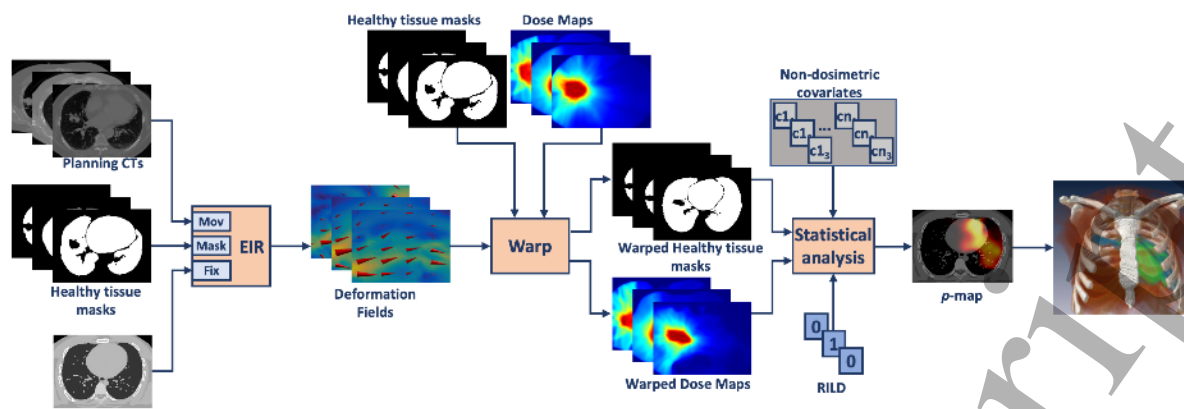
#### **3D voxel-wise outcome mapping**

1  
2  
3 669 DVMs (Section 2.2.4) can be generated either starting from an anatomical structure and restricted to  
4  
5 670 its volume or independently from any structure. The second choice has the power to embrace a  
6  
7 671 totally agnostic approach regarding which organs/tissues are involved in radio-induced toxicity and  
8  
9 672 entails the possibility of highlighting the interaction between different organs and FSUs. Notably,  
10  
11 673 special care should be taken in order to counteract the possibility of finding significant areas which  
12  
13 674 offer no feasible anatomical explanation and which could lead to inappropriate organ-sparing  
14  
15 675 objectives in treatment planning.

16 676 Organ-based DVMs were considered in the literature for the analysis of both rectal (Acosta *et al.*,  
17  
18 677 2013; Drean *et al.*, 2016b; Mylona *et al.*, 2020b; Shelley *et al.*, 2017; Marcello *et al.*, 2020b) and  
19  
20 678 urinary (Mylona *et al.*, 2019; Mylona *et al.*, 2020a; Mylona *et al.*, 2020b; Marcello *et al.*, 2020a)  
21  
22 679 toxicity. These kinds of analysis heavily build upon robust co-registration methods, which become  
23  
24 680 even more critical when organs highly prone to organ motion and variable filling are considered.

25 681 The first published example of the use of quasi-organ-agnostic DVMs was from Heemsbergen *et al.*  
26  
27 682 (2010) investigating urinary toxicity. In this case, the 3D reconstruction started with the definition of  
28  
29 683 the outer surface of the prostate and with the identification of the spatial coordinates of the  
30  
31 684 prostate centre of mass. After that, for every patient, a spherical surface was considered, extending  
32  
33 685 6 cm from the prostate. Every voxel inside this region was identified through polar coordinates  
34  
35 686 (distance from the prostate centre of mass and two angles identifying the vector connecting the  
36  
37 687 single voxel to the prostate centre of mass) and the absorbed dose in each voxel was calculated by  
38  
39 688 trilinear interpolation of the nearest dose points of the individual dose grid.

40 689 Regression coefficients associated to each voxel specifically in the salivary glands have been used to  
41  
42 690 shed light on the regional radio-sensitivity of the glands (Jiang *et al.*, 2019). Other studies considered  
43  
44 691 DVMs without any restriction to specific contoured organs for investigation of local dose effects in  
45  
46 692 the thoracic/head and neck region (Beasley *et al.*, 2018; McWilliam *et al.*, 2017; Monti *et al.*, 2017;  
47  
48 693 Palma *et al.*, 2016; Palma *et al.*, 2019d; Palma *et al.*, 2019c; Green *et al.*, 2020), with interest in the  
49  
50 694 association of dose pattern with lung toxicity, acute dysphagia, trismus and survival.  
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695

696 **Figure 6: Flowchart for 3D voxel-wise analysis of dosimetric association with lung toxicity following stereotactic body**  
 697 **lung radiotherapy, reproduced from Palma *et al.* (2019c). Structures and dose distributions are spatially normalised to a**  
 698 **common coordinate system (CCS) via course alignment of structures and CT elastic image registration (EIR). Voxel-wise**  
 699 **significance maps are then derived by calculating a test statistic at the voxel level and adjusting for multiple comparisons**  
 700 **via a permutation algorithm.**

### 701 ***NTCP from voxel-wise methods***

702 As already pointed out, although voxel-wise analysis can identify important organ sub-regions, it  
 703 does not provide an NTCP.

704 NTCP can be derived by classical dose-response modelling on the specific sub-regions, either  
 705 including the whole DVH as calculated in the specific identified areas or choosing some particular  
 706 DVH cut-points. Examples of this kind of approach can be found in (Buettner *et al.*, 2009b;  
 707 Heemsbergen *et al.*, 2010; Mylona *et al.*, 2019; Onjukka *et al.*, 2019; Palma *et al.*, 2016; Casares-  
 708 Magaz *et al.*, 2017). In Drean *et al.* (2016b), parameters for the LKB model were computed within  
 709 the voxel-wise derived sub-region.

710 More sophisticated and more global approaches were also developed, taking information from  
 711 voxel-wise analysis directly into account. Vinogradskiy *et al.* (2012) proposed a modified LKB model  
 712 where the lung dose in each voxel was weighted using a user-defined spatial weighting matrix which  
 713 could be derived by a previous voxel-wise analysis. Jiang *et al.* (2019) demonstrated prediction of  
 714 xerostomia induced by the irradiation of the salivary glands in head-and-neck cancer patients using a  
 715 ridge logistic regression model directly dealing with the local dose delivered to each voxel of the  
 716 organ at risk. The framework was naturally able to include non-dosimetric predictors in the NTCP  
 717 model.

718 Palma *et al.* (2019a) established a new formalism, called PACE (Probabilistic Atlas for normal tissue  
 719 Complication Estimation in radiation therapy), which incorporates regional dose information coming

60

1  
2  
3 720 from regression performed at the voxel-wise with clinical risk factors. PACE builds upon the LKB  
4  
5 721 model and substitutes the generalized equivalent uniform dose (EUD) with a weighted combination  
6  
7 722 of risks as calculated by regression at the voxel level, using confidence intervals for predicted risks as  
8  
9 723 weights (thus giving more weight to more certain predictions).

## 11 724 **5.3 Spatial parameterisation of dose distributions**

### 14 725 *5.3.1 Description*

16 726 Attempts to reduce the number of features, reduce collinearity and generalise models from voxel-  
17  
18 727 wise analyses can be made by parameterising the dose distribution. For analyses restricted to  
19  
20 728 specific organs, this will typically involve functional parameterisation of DSMs and organ-constrained  
21  
22 729 DVMs, with or without registration to a template geometry. The resulting parameters can then  
23  
24 730 become co-variates in regression models or supervised machine learning models. More widespread  
25  
26 731 dose distributions can be parameterised using techniques borrowed from imaging analytics –  
27  
28 732 namely, the supervised derivation of specific feature classes (“dosimics” (Liang *et al.*, 2019)).  
29  
30 733 Unsupervised classification of outcome based on the dose distribution can also be attempted with  
31  
32 734 convolutional neural networks, with or without the inclusion of anatomical and functional imaging  
33  
34 735 information.

### 34 736 *5.3.2 Examples*

#### 37 737 ***Parameterisation of 2D dose***

38 738 The process of derivation of parameters for geometric descriptors from a DSM is illustrated in Figure  
39  
40 739 2, particularly in the context of investigating rectal complications due to prostate radiotherapy.  
41  
42 740 Concentric isodoses on the rectal wall from prostate radiotherapy can be thresholded systematically  
43  
44 741 at different doses and fitted with an ellipse. Parameterised geometrical features can then be  
45  
46 742 calculated (Buettner *et al.*, 2009b).

47  
48 743 Previous studies on rectal toxicity following prostate radiotherapy indicate that spatial dose metrics  
49  
50 744 such as lateral extent of dose around the circumference of the rectum, longitudinal extent and  
51  
52 745 eccentricity derived from rectal dose surface maps (DSM), are related to toxicities including rectal  
53  
54 746 bleeding and loose stools (Buettner *et al.*, 2009b; Moulton *et al.*, 2017). Interestingly, a recent test of  
55  
56 747 this approach failed to demonstrate any improvement over DVH-based prediction of rectal toxicity  
57  
58 748 (Wilkins *et al.*, 2020). This result may be confounded by the differences between planned and  
59  
60 749 delivered dose distributions (see Section 3.1.3), with Shelley *et al.* (2017) finding parameters derived

1  
2  
3 750 from DSMs for accumulated dose being more predictive than those from planned dose, as also  
4  
5 751 found by Casares-Magaz *et al.* (2019) at the pixel-level.

6  
7  
8 752 Casares-Magaz *et al.* (2017) demonstrated that parameterised DSMs performed slightly better than  
9  
10 753 DSHs when predicting rectal toxicity and produced results for more endpoints by quantifying the  
11  
12 754 dose when a DSM was subdivided to a 3x3 matrix. Vanneste *et al.* (2018) used DSMs to evaluate the  
13  
14 755 effect of hydrogel rectal spacers on dose to the rectum for prostate radiotherapy.

15  
16 756 Although most published data relating to parameterised rectal DSMs is from patients who received  
17  
18 757 prostate radiotherapy, Chen *et al.* (2018) detail the use of DSM to relate the dose from both external  
19  
20 758 beam and brachytherapy for a cohort of cervix patients. The two dose distributions were non-rigidly  
21  
22 759 registered, and a rectal DSM created from the summed dose distribution. Both volumetric and  
23  
24 760 texture metrics were calculated, and principal component analysis used to provide inputs to a  
25  
26 761 support vector machine-based model. Area and texture parameters were found to be important and  
27  
28 762 to have an improved AUC compared to the standard Groupe Européen de Curiethérapie/European  
29  
30 763 Society for Radiotherapy (GEC-ESTRO) model.

#### 31 764 ***Parameterisation of 3D dose***

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33 765 For a solid structure such as the parotid it is possible to define metrics to quantify the relative 3D  
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35 766 spatial distribution of dose to the whole organ. Buettner *et al.* (2012b) used 3D spatial invariant  
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37 767 moments to characterise the morphology of the dose distribution to the parotid in terms of centre  
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39 768 of mass, spread and skewness. They showed that minimising the dose to cranial and lateral regions  
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41 769 of the parotid gland would decrease the incidence of xerostomia. The model containing spatial  
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43 770 metrics had a significantly-improved performance compared to the standard predictive of model of  
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45 771 mean dose. 3D moments were also used in a comparison of the conventional oral mucosa outline  
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47 772 and a novel segmentation to predict acute mucositis (Dean *et al.*, 2016). Dose distributions to the  
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49 773 two organ-at-risk (OAR) structures were calculated and used as inputs to both penalised logistic  
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51 774 regression and random forest models. In this example, using the novel segmentation and spatial  
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53 775 metrics did not improve model performance compared to a model built on fractional dose-volume  
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55 776 data for the conventional structure. (Dean *et al.*, 2018) studied acute dysphagia using moments and  
56  
57 777 dose-volume-length and -circumference data for the pharyngeal mucosa. They demonstrated that  
58  
59 778 although the length and circumference that received over 1 Gy per fraction were shown to be  
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779 important, a penalised logistic regression NTCP model trained purely on dose-volume data  
780 performed equally well on internal validation and was superior when applied to an external  
781 validation cohort.

### 782 ***Supervised broad spatial descriptors***

783 The papers described so far have used a variety of bespoke methods to parameterise the spatial  
784 distribution of dose. However, synergy with the field of radiomics allows spatial dose distributions  
785 to be characterised by a vast array of standardised metrics (Zwanenburg *et al.*, 2020). Here the 3D  
786 radiotherapy dose distribution can be characterised in full with or without reference to structure  
787 segmentation. Radiomic features from patient images can be integrated to derive models predictive  
788 of complication (Talamonti *et al.*, 2019).

789 One study which assessed this concept and compared predictions to previous work is described by  
790 Gabryś *et al.* (2018). This study compared models to predict xerostomia starting with a standard  
791 model based on mean dose and parotid-specific spatial metrics described above (Buettner *et al.*,  
792 2012b). Spatial descriptors were extended for the parotid gland to consider entropy along with  
793 dosiomic descriptors of DVH shape and general dosiomic features describing the gradient of the  
794 entire 3D dose distribution. The manuscript describes comparisons of many models including  
795 conventional statistical and machine learning approaches. Additionally, feature selection and class  
796 balance approaches were compared. Overall the strongest features identified were parotid gland  
797 volume eccentricity and the spread of the contralateral parotid dose distribution. The contralateral  
798 dose gradient of the 3D dose distribution (right to left) was also identified on univariate analysis but  
799 did not feature strongly in the final multivariate analysis. Similarly, Lee *et al.* (2020) informed  
800 machine learning algorithms with combinations of dose-volume, radiomics and dosiomics features,  
801 together with clinical co-variates. Resulting predictive models of weight loss in lung cancer  
802 radiotherapy with greater accuracy than models based on dose-volume and clinical co-variates  
803 alone, though still with a relatively modest AUC of 0.71.

804 Liang *et al.* (2019) compared conventional dosimetric models with models derived from dosiomic  
805 features to predict radiation pneumonitis. It was demonstrated that a multivariate NTCP model  
806 including the Grey Level Co-occurrence Matrix (GLCM) contrast and Grey Level Run Length Matrix  
807 (GLRLM) (which has similarities to lateral and longitudinal extent described previously)  
808 outperformed models based on dose-volume parameters and conventional NTCP model parameters.  
809 Rossi *et al.* (2018) included texture analysis features in a study to predict genitourinary and  
810 gastrointestinal toxicity following prostate radiotherapy. The 3D texture analysis features for the  
811 rectum and bladder were derived from standard radiomics and used alongside non-treatment  
812 related features (such as age, staging and comorbidities) and DVH-based metrics to build  
813 multivariate logistic regression NTCP models. It was demonstrated that for gastrointestinal  
814 endpoints inclusion of texture features improved the AUC compared to models containing only

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3 815 clinical and DVH-based features. Results for genitourinary toxicity were generally not improved by  
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5 816 any dosimetric features.  
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### 8 817 ***Unsupervised broad spatial descriptors***

9 818 An alternative to utilising crafted dosimetric descriptors of broad distributions is to apply neural  
10 819 networks. For example, Buettner *et al.* (2009a) used DSMs derived by the rectum unfolding as input  
11 820 for a rectal bleeding model based on locally-connected neural networks able to account for the  
12 821 topology of the dose distribution. The higher performance achieved by such models, compared to  
13 822 the more traditional fully-connected conventional neural nets based on DSHs, suggested that  
14 823 morphological aspects of the dose distributions play a relevant role in the development of radiation  
15 824 induced morbidity. Zhen *et al.* (2017) utilised a convolutional neural network (CNN) to distinguish  
16 825 rectal DSMs indicative of toxicity, incorporating transfer learning to compensate limited patient  
17 826 data.  
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25 827 CNNs can be used to extract unspecified higher-level features of 3D dose distributions which can  
26 828 directly classify the distributions as likely to lead to complications, and studies have begun to emerge  
27 829 demonstrating this with varying combinations of ancillary information. Ibragimov *et al.* (Ibragimov *et*  
28 830 *al.*, 2018; Ibragimov *et al.*, 2019) utilised CNNs incorporating 3D dose information, supplemented  
29 831 with transfer learning from previous abdominal imaging, for hepatobiliary toxicity prediction  
30 832 following stereotactic liver radiotherapy. Incorporating the CNNs with more conventional features  
31 833 including dose-volume parameters, dose-fractionation and clinical co-variables increased the model  
32 834 predictions (increase in AUC from 0.79 to 0.85). In a strategy which preferences identifying likely  
33 835 toxicity (i.e., minimising false negatives), the CNN approach halved the number of false positive  
34 836 predictions relative to DVH-based prediction. Ibragimov *et al.* were able to extend this approach to a  
35 837 structure-agnostic spatial assessment to map anatomical regions where dose variations associate  
36 838 with toxicity. This revealed regions associated with the hepatobiliary tract and liver as specific focus  
37 839 regions to guide dose planning (Ibragimov *et al.*, 2020).  
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48 840 In a progression from the dosimetrics approach, Liang *et al.* (2020) utilised CNNs incorporating the 3D  
49 841 dose distribution for predicting pneumonitis following volumetric-modulated radiotherapy. A  
50 842 superior prediction (AUC 0.842) was achieved relative to regression models incorporating  
51 843 dosimetric, NTCP and dosimetrics features (AUC < 0.782). Class activation maps were used to identify  
52 844 lung regions associated with increased or reduced high-grade toxicity.  
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58 845 In head and neck cancer radiotherapy, Men *et al.* (2019) used CNNs which incorporated one or more  
59 846 of the planning CT images, planned 3D dose and segmented anatomy, for prediction of grade  $\geq 2$   
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3 847 xerostomia, and compared prediction against regression models incorporating dose with or without  
4 848 clinical co-variates. The CNNs provided greater accuracy ( $AUC < 0.84$ ), compared to the regression  
5 849 models, for all combinations of 3D information except for when 3D dose was removed.  
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## 9 850 **5.4 Spatial clustering**

### 11 851 *5.4.1 Description*

12 852 Thames *et al.* (2004) proposed that hot spots distributed as small areas throughout an organ at risk  
13 853 are likely to cause a different response than if the highest dose covers one contiguous region. This  
14 854 difference would translate through to a difference in toxicity prediction using NTCP models which  
15 855 describe the clustering of damage to FSUs. This concept of spatial dose clusters forms bridges  
16 856 between voxel-wise assessment, definition of sub-regions and spatial analysis based on spatial  
17 857 parameterisation. The cluster models highlight the relevance of including both the number and the  
18 858 spatial location of radiation-sterilized FSUs in a comprehensive NTCP model (Thames *et al.*, 2004). In  
19 859 a general sense, these models suggest that a volume receiving at least a given dose value is more  
20 860 likely associated with a radiation-induced toxicity if it corresponds to a connected spatial cluster  
21 861 rather than if spatially scattered (Deasy and El Naqa, 2008).  
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### 32 862 *5.4.2 Examples*

33 863 Tucker et al demonstrated a practical application of the method described by Thames using rectal  
34 864 DSMs (Tucker *et al.*, 2006b). Nine case-control pairs with very similar absolute DSH but with and  
35 865 without grade 2 rectal bleeding were used to fit a local-effect cluster model. The logistic function  
36 866 describing the probability of damage for each voxel in each DSM had 2 unknown parameters. The  
37 867 model was fitted to maximise the relationship between maximum cluster size (considering 2-  
38 868 connectivity) between the cases and controls. Although the cohort was very small, the authors were  
39 869 able to find parameter values which separated cases from controls and inferred that dose  
40 870 distributions in the region of 30 Gy were important for the prediction of rectal bleeding.  
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48 871 Chao et al (Chao *et al.*, 2020; Chao *et al.*, 2018) also developed spatial cluster metrics based on the  
49 872 method proposed by Thames et al. They demonstrated that maximum cluster size for the superior 5  
50 873 cm of the oesophagus was not related to conventional dose-volume and NTCP metrics and inferred  
51 874 that spatial distributions were not represented by conventional dose metrics. They applied a cluster-  
52 875 based approach to model xerostomia (Chao *et al.*, 2019). The metrics included mean cluster size and  
53 876 largest cluster size normalised to the volume of the gland which were incorporated into LKB models.  
54 877 Although no conventional (DVH-based) LKB model was derived from the cohort a comparison was  
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878 made with published models utilising mean dose ( $n=1$ ). TD50 was higher for the thresholded cluster  
879 model at just below 40 Gy compared to 26 Gy from the literature.

880 The concept of spatial cluster models can be expanded using percolation theory, which has origins in  
881 statistical physics and considers how clusters are connected. Originally proposed at a similar time to  
882 Thames' (Thames *et al.*, 2004) work on cluster models, Myers and Niemierko (2004) presented the  
883 use of percolation theory for predicting NTCP from clusters. Gale *et al.* (2017) describe how the  
884 concept can be applied to geometric arrangements of FSUs to predict toxicity for both parallel and  
885 serial organs.

886 Several studies considered the clusters of organ voxel  $L_p^-$  whose dose-toxicity association exceeded  
887 some statistical significance threshold  $p$ . They showed that the mean dose in such clusters could be  
888 a more powerful predictor of toxicity than traditional metrics associated to the organ considered as  
889 a whole structure. Hence, an NTCP model can be proficiently trained as a logistic regression of the  
890 patients' outcomes as a function of simple dose metrics in the cluster  $L_p^-$  propagated from the  
891 common coordinate system of the voxel-wise analysis (see Section 5.2) to each individual native  
892 space. In this way, sub-regions have been identified in different locations such as the lungs (Palma *et al.*  
893 *et al.*, 2016), the heart (McWilliam *et al.*, 2017), head and neck (Monti *et al.*, 2017), the rectum (Acosta  
894 *et al.*, 2013; Drean *et al.*, 2016b) and the bladder (Mylona *et al.*, 2019).

## 895 **6 Ongoing Endeavours**

### 896 **6.1 Model development and validation**

897 As for other approaches to radiotherapy complication modelling, a major issue is represented by the  
898 quantity and quality of data available to researchers. Relative to DVH-based models, spatial methods  
899 require more comprehensive data (see Section 3). Despite the abundance of relevant data  
900 generated continuously around the world and the technical capability to collect it, and despite  
901 decades of pleas (e.g. (Deasy *et al.*, 2010)), remarkably little data has become available to progress  
902 this type of analysis. Based on legislative constraints (i.e., ownership, privacy and patient consent  
903 needs) it is likely, at least in the next few years, that data will prevalently come from clinical trials  
904 where their recovery, storage and access are already planned.

905 The implementation of innovative trials including large cohorts of clinical data (Baumann *et al.*,  
906 2016) could rapidly change the landscape. Such trials could multiply the opportunities for developing  
907 models, provide opportunities for validating models, and enable the merging of different large  
908 cohorts to increase feature diversity. A specific issue may concern the possibility of introducing

909 unpredictable biases if pooling together cohorts of patients treated, for instance, at different dose  
910 levels with largely different spatial locations of the high-dose volumes. Uncontrolled voxel-wise  
911 comparisons could lead to “false” spatial effects due, for instance, to the higher incidence or  
912 prevalence of side effects in cohorts delivering systematically higher doses and/or treating larger  
913 volumes. Ideally, the availability of large cohorts should be accompanied by a proper grouping of  
914 patients to make the different patient groups comparable.

## 915 **6.2 Model generalisation and extension**

916 Apart from the critical issues related to generalizability of NTCP models such as technical, temporal  
917 or geographical variabilities (van der Schaaf *et al.*, 2015), a few specific points deserve discussion.

918 The interplay between the spatial patterns of a certain modality/technique and the inter-individual  
919 variability is a challenging issue: well driven studies may help in quantifying the real impact of a  
920 modality with respect to another. The generalizability of models across different modalities need  
921 high-quality studies and extensive validation. One confounding problem is that the patterns of dose  
922 delivered today already reflect the existing knowledge based on dose volume metrics. As these  
923 models mature, there is the potential for radiobiological predictions that consider the spatial pattern  
924 of dose that can drive the optimization of treatment plans towards more favourable dose patterns  
925 beyond that of the traditional dose-volume metrics.

926 Another important field of investigation regarding model generalisation is represented by the  
927 challenge of combined therapies. Data from studies testing radiotherapy-only vs combined therapy  
928 (for instance chemotherapy, immunotherapy) could help in assessing spatial dosimetry correlations  
929 specifically linked to the action, for instance, of a drug and making possible local dose corrections  
930 incorporating its effect. Similarly, highly non-conventional dose and dose-rate distributions, such as  
931 from ultra-fast irradiation (Esplen *et al.*, 2020) or molecular radiotherapy (Stokke *et al.*, 2017) will  
932 offer new data sources with which to generalise derived models.

## 933 **6.3 Including intra and inter-fraction changes**

934 In many situations, both intra and inter-fraction anatomical and geometrical changes may have a  
935 significant impact in modifying the delivered dose with respect to the planned one. In particular, the  
936 prevalence of systematic over random changes may potentially blur (or even hide) the correlation  
937 with toxicities; consequently, investigations quantifying these effects are needed. As an example,  
938 the impact of variable bladder filling on bladder DSM can be assessed from daily cone-beam CT  
939 imaging: one recent study showed a relatively small impact of variable filling on bladder DSM during  
940 image-guided radiotherapy of prostate cancer (Palorini *et al.*, 2016a). A statistical approach based on

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3 941 Gaussian-like variations of local doses likely works in several situations but is expected to fail in  
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5 942 others, such as when the phenomenon itself is prevalently non-Gaussian. Shelley *et al.* (2017)  
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7 943 demonstrated superiority in toxicity prediction from rectal DSMs formed from estimated delivered  
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9 944 rather than planned dose.

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11 945 When the toxicity rate is small (say, <10%), those few patients with large systematic changes  
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13 946 resulting in a relevant increase of dose to proximal OARs may jeopardise results. Greater efforts may  
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15 947 especially be expected in trying to incorporate individually-assessed anatomical modifications in  
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17 948 stereotactic body radiation therapy (SBRT) (Magallon-Baro *et al.*, 2019), looking to the 3D dose-of-  
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19 949 the-day and/or to the accumulated dose instead of the planned dose distribution. SBRT is also prone  
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21 950 to be associated with larger effects due to both the reduced margins and the high dose per fraction,  
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23 951 dealing with an enhanced impact on critical regions even with small anatomical/geometrical  
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25 952 changes. Relevant effects due to systematic deviations between the planned and the delivered dose  
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27 953 may occur even in unexpected situations and the availability of in-room imaging information is of  
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29 954 paramount importance to identify them. The recently reported correlation between shift toward the  
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31 955 heart of field isocentre during delivery and poorer survival in lung cancer patients treated with SBRT  
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33 956 is a highly paradigmatic example (Johnson-Hart *et al.*, 2018).

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35 957 Similarly, intra-fraction changes are known to significantly affect the delivered dose in specific sites.  
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37 958 Breathing-induced motion can be highly anisotropic and variable between patients in the different  
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39 959 thoracic and abdominal areas. Although, to our knowledge, no studies have reported on the impact  
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41 960 of intra-fraction motion on spatial models, more relevant research in this area is needed.

#### 42 961 **6.4 Potential applications of artificial intelligence**

43 962 The rise of deep learning approaches for image segmentation, pattern recognition and patient  
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45 963 classification adds many opportunities to extend this field (El Naqa and Das, 2020). Ready access to  
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47 964 advanced deep learning tools is making this kind of analysis more popular (with examples given in  
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49 965 Section 5.3). A merit of these methods is the opportunity to consider features mostly “hidden” to  
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51 966 the human eye and to find complex correlations in a multi-layer approach. On the other hand, this  
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53 967 same merit may also constitute a disadvantage from the point of view of interpretability of the  
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55 968 results and consequent confidence in clinically applying them; in fact, any attempt to maintain some  
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57 969 causality to explain any correlation is largely lost. A major issue regarding artificial intelligence  
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59 970 models is their intrinsically higher difficulty in being validated. Valdes and Interian (2018) provide a  
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971 timely summary of the potential for mis-interpretation in such complex approaches. Keeping the  
972 models as simple and interpretable as possible should be considered valuable: the benefit of the

973 addition of deep learning based spatial signatures should always be demonstrated and quantified in  
974 validation cohorts.

## 975 **6.5 Understanding pathophysiology**

976 An intriguing and relevant field of investigation related to NTCP models based on 3D/2D similarity  
977 comparisons concerns the meaning of the resulting regions whose dose differences are predictive of  
978 toxicity. As already underlined, the information resulting from these analyses cannot be  
979 automatically associated to a specific cause, being intrinsically a phenomenological finding (i.e.:  
980 simply reflecting some statistical correlation). Moreover, the assessment of specific  
981 volumes/surfaces within the body/OARs apparently more “sensitive” to radiation can be biased by  
982 unknown factors or just due to geometrical or technical issues. Any hypothetical causality has to be  
983 considered as a strength of such models, in case the found results are consistent with known  
984 physiological processes/functionalities. As examples, identification of the bladder trigone as a  
985 structure likely to be highly sensitive (Rancati *et al.*, 2017; Henderson *et al.*, 2018; Yahya *et al.*, 2017)  
986 is consistent with the involvement of the trigone in the physiology of urination, and the physiological  
987 connection between the heart and lungs (Ghobadi *et al.*, 2012) adds validity to correlation of heart  
988 dose with lung toxicity (Palma *et al.*, 2019c; Palma *et al.*, 2019d). Any hypothesis generated by such  
989 models would deserve to be tested in pre-clinical and clinical studies. Animal models may be well  
990 used to verify the existence of spatial effects. Conversely, pre-clinical research may first explain  
991 specific patterns of toxicity that may be confirmed later by studies dealing with dose similarity  
992 comparison. An interesting example is the evidence of spatial dosimetry effects within parotids  
993 impacting xerostomia, due to the sparing (or not) of stem cells contained in the ductal region. Such  
994 observations have been reported in animal experiments (van Luijk *et al.*, 2015) and confirmed by a  
995 3D dose comparison investigation on data from a large patient cohort treated for head-neck cancer  
996 (Jiang *et al.*, 2019).

## 997 **6.6 Model application**

998 Although examples of practical applications of NTCP models incorporating spatial dosimetric  
999 features are rare, it is likely that a few of the most robust results will increasingly influence planning  
1000 optimization. When a causal relationship between a spatial effect and the pattern of the  
1001 corresponding side effects is apparent, changes may be easily implemented in clinical practice. Two  
1002 examples are the previously-cited cases of the bladder trigone for prostate cancer and the ductal  
1003 region of the parotid glands. The latter, cited above as originating in pre-clinical studies, is being  
1004 assessed within a clinical trial (van Luijk *et al.*, 2015), which is probably the first example of a trial

1005 specifically looking to the possibility to exploit information regarding the spatial dose distribution  
1006 within an OAR to reduce toxicity.

1007 A likely progression will be the incorporation of spatial models into tools to evaluate the planned 3D  
1008 dose distribution and for generating NTCP and risk estimates. This could be accomplished, for  
1009 instance, within clinical trials or as an additional tool for plan quality assurance, in complement with  
1010 conventional DVH-based EUD/NTCP estimates. The propagation of identified sensitive sub-regions to  
1011 an individual would facilitate toxicity-minimised planning, without the need to modify current  
1012 optimisation methods (Acosta and De Crevoisier, 2019). This has been demonstrated by Lafond *et al.*  
1013 (2020). A subsequent natural extension would be the possibility to implement these models directly  
1014 into the optimization engine. However, the general adoption of spatial models is greatly inhibited by  
1015 the prior evolution of the planning process and optimisation engines in the context of dose-volume  
1016 approaches. For spatial models that cannot be formulated via dose-volume terminology, research  
1017 planning systems are required to enable inclusion of the relevant predicted complication models in  
1018 optimisation constraints and objectives or via scripting capabilities of commercial planning systems  
1019 (e.g. (Voutilainen, 2016)). With the growth of artificial intelligence based planning systems, there is  
1020 considerable scope for building automated planning algorithms that directly incorporate spatial  
1021 models to augment or replace dose-volume based optimisation (Wang *et al.*, 2019).

1022 Intriguingly, for models which are agnostic to segmented structures, plan optimisation could in  
1023 principle be feasible without the incorporation of dose-volume data for OARs. This would permit a  
1024 segmentation-free plan optimization. In the same direction, this kind of approach could also find  
1025 applications in overall treatment optimization, directly considering patient outcome as the goal and  
1026 incorporating possible “systemic” effects due to the irradiation of multiple organs and to the  
1027 interaction with the immune system (for instance through the implicit consideration of the  
1028 incidental irradiation of nodes and of the vascular system). Similarly, one could hypothesize  
1029 applications in combined treatments to include the effect of modifying agents at the voxel-level, and  
1030 to “virtual human” simulation in the optimisation of patient-specific treatments.

## 1031 **7 Conclusion**

1032 The field reviewed in in this paper is still in its infancy. However, models which consider the spatial  
1033 characteristics of radiotherapy dose will permit the expansion, or at least fine-graining, of the  
1034 solution space for radiotherapy treatment planning and improving the prediction of treatment  
1035 complications. The potential for large-scale relevant applications in treatment personalization, plan

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3 1036 optimization and evaluation are more than promising. Rapid developments and extensive  
4 applications are expected in the coming years.  
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