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Winter is over: The use of Artificial Intelligence to individualise radiation therapy for breast cancer☆

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ABSTRACT

Artificial intelligence demonstrated its value for automated contouring of organs at risk and target volumes as well as for auto-planning of radiation dose distributions in terms of saving time, increasing consistency, and improving dose-volumes parameters. Future developments include incorporating dose/outcome data to optimise dose distributions with optimal coverage of the high-risk areas, while at the same time limiting doses to low-risk areas. An infinite gradient of volumes and doses to deliver spatially-adjusted radiation can be generated, allowing to avoid unnecessary radiation to organs at risk. Therefore, data about patient-, tumour-, and treatment-related factors have to be combined with dose distributions and outcome-containing databases.

1. Introduction

Breast cancer is a leading cause of cancer death in women, even though the vast majority of patients have non-metastatic disease at diagnosis [1]. An estimated number of 2,088,849 new cases of female breast cancer were diagnosed worldwide in 2018, representing 11.6% of all cancers, which poses a major burden on health care economics, time, and human resources [1]. Oncology aims to improve patient outcome, not only in terms of survival, but also by reducing treatment-related toxicity and improving quality of life.

To assure good patient care, consensus-based guidelines are developed to provide criteria and thereof derived quality indicators [2]. Continued developments in basic research, diagnostics, and therapeutics demand an ever-growing level of knowledge and skills that is becoming overwhelming for many health care providers. One of the solutions to meet this challenge comes from the integration of Artificial Intelligence (AI) in medical applications.

AI is a term used to describe the mimicking by computers of *cognitive* functions that we associate with human thinking processes, including *learning* and *problem solving* [3]. Currently, it has applications in several fields including electronics, mathematics, statistics, computer science, biology, neural network, game theory, linguistics, robotics, internet, humanities research, and progressively enters the field of health care [3].

Already in ancient times, philosophers engaged in the idea of charming machines assisting humans in decision-making. Early advances included developments in language understanding, translation, theorem proving, and knowledge-based systems aimed to assist in problem-solving by incorporating continuous inflow of information from difference sources [4].

A subset of AI including the advanced automation of machine

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learning (ML) – incorporating *big data* to assist in decision-making processes – was presented to the medical community over six decades ago [5,6]. As these developments were challenged by limited technological means, it evolved from a promising field of *fantasies, possibilities, demonstrations, and promise* [4], to a subject of scepticism and lack of funding, known as *The Winter of AI* [3].

AI is introduced in health care to assist providers, for example to help define the most appropriate treatments, in the field of oncology [7]. AI is expected to take a pivotal role in future developments of medical fields that are mainly dependent on technology and imaging, including radiation oncology (RO), without obviating the role and human aspects of involved health care providers. As a subset of ML, deep learning (DL) is based on artificial neural networks and is able to automatically extract hierarchical features of multiple source data to use them in different clinical applications, including imaging, volume contouring, and treatment planning [8,9]. AI and DL are progressively integrated in breast cancer diagnosis including imaging and pathology [10]. Data from multiple sources (mammography, ultrasound, CT, MRI, pathology, surgical reports, radiation therapy, follow-up imaging) are processed by bioinformatics technology to predict outcomes and to guide multidisciplinary therapeutic approaches, including radiation therapy (RT). Risk assessment algorithms, using information on geometrical, temporal, and spatial variations of recurrence risks as well as on toxicity and cosmetic outcomes will be integrated to guide treatment planning algorithms, to optimise treatment choices, and – thereby – outcomes [11].

We aim to discuss expected developments in AI for breast cancer patients, focusing on the RO treatment planning process, including the optimisation of dose distribution based on spatial patterns of loco-regional relapses, and the assessment of clinical outcome prediction models.

2. AI in breast cancer RT planning

The preparation of actual RT delivery involves several steps that use data from multiple sources, including images, treatment prescription algorithms, and dose-volume parameters for target volumes and organs at risk (OARs). While the human component is essential to guide this process, most steps of this workflow contain repetitive tasks that are time-consuming and prone to errors as well as intra- and inter-observer variability (Fig. 1). Currently available AI technology is progressively being introduced to assist the radiation community to improve this important part of breast cancer care.

2.1. Automated target volume contouring

In contrast to primary tumours such as head & neck and lung cancer, target volume contouring methods for breast cancer are still mostly based on *conventional* field-based and 2-dimensional RT treatment techniques [12]. However, modern RT should be based on anatomical definitions of target volumes, taking into account the actual loco-regional recurrence risks, to individualise treatment planning and to optimise dose distributions minimising doses to OARs, such as heart and lungs [13]. Even though contouring targets within a predefined set of volumes is a straightforward easy task, the process of anatomically individualised targets contouring is highly demanding in terms of time and expertise, mostly due to the high burden of breast cancer patients in RT departments. Therefore, adopted solutions included delegation of routine contouring to radiotherapy technologists (RTT) and automated segmentation algorithms' use.

Auto-segmentation was originally used for OARs contouring recognisable by a distinct tissue density, including liver, lungs, spinal cord, and kidneys. Later, atlases for volume contouring of normal tissue have been integrated in more advanced auto-contouring systems [14]. For auto-segmentation of target volumes, either distinct tissue densities (like lung cancer surrounded by normal lung tissue) and/or well-defined contouring atlases (first available for head & neck cancer) are required [15]. Recently evaluated software used atlas-based segmentation (ABS), alone or in combination with model-based segmentation (MBS) [16–18]. Both ABS and MBS were integrated in ML methods [19], referred to as DL [20,21], to continuously improve automated target volumes contouring [22,23].

These DL algorithms used neural networks to identify and generate contouring patterns to be combined with information from multiple sources, in order to generate volumes on CT-images that can subsequently be validated for RT dose planning by the physician. DL-based contouring has been widely explored in head & neck, lung, and prostate cancer, showing important benefit in terms of time-sparing combined with an improved inter- and intra-observer contouring variability [17,24–29].

It is worth spending time validating the atlas contours, since an ABS/MBS system will never work if local contouring practices differ from those used to define the atlas [16]. Automated contouring using AI through DL algorithms for breast cancer has not been widely introduced in clinical practice yet, although several published experiences showed how it could significantly reduce contouring variation among physicians, even in case of different patient body shapes and treatment positioning [30–32]. Pre-segmented contours using deformable registration software are based on a patient model with a consensus contour definition [22,33]. Poor agreement for the delineation of small-sized volumes – including the interpectoral and internal mammary nodal regions and the left anterior descending coronary artery – was demonstrated using ABS-based auto-segmentation [31]. Ciardo et al. [34] analysed the efficacy of ABS with simultaneous performance level estimation (STAPLE algorithm), showing poor performance of ABS alone particularly for the oesophagus, stomach, brachial plexus, and supraclavicular nodal contouring, with an improved performance when adding the STAPLE algorithm [18].

As the quality of auto-segmentation is largely dependent on the algorithms used and the information fed into the system, improving data entered to the system by high-numbers of high-quality delineations with less variability will improve its performance. Improving physician's contouring skills by participating in dedicated courses, such as those offered by the European SocieTy for Radiotherapy & Oncology (ESTRO) - FALCON (Fellowship in Anatomic delineation and CONtouring) [35], and gaining experience with internationally endorsed atlases [13,36–38], is essential for improving DL and auto-segmentation skills. Experience and anatomical knowledge is also required to supervise the outcome and to individualise contouring for each patient. Therefore, the *final touch* of the contouring process will remain a human-based, with technology in a supportive role.

New promising AI technologies are being developed to highly train radiation oncologists. Mak et al. [39], organising a contest for an international community of programmers, demonstrated that combined crowd innovation with AI led rapidly to automated algorithms able to replicate manual lung tumour segmentations of an expert radiation oncologist. As these developments are finding their way to routine applications, it is time to facilitate this process by delineating all target volumes in breast cancer using common atlases [13,38], both to gain experience and to improve our skills, as

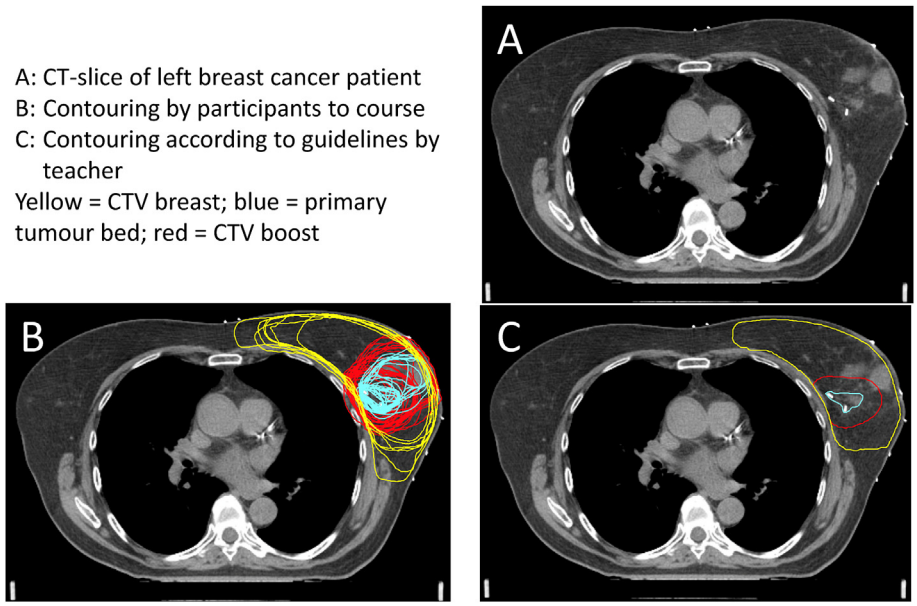

Fig. 1. Target volume contouring variation. A: CT-slice of left breast cancer patient; B: Contouring by participants to course; C: Contouring according to guidelines by teacher. Yellow = CTV breast; blue = primary tumour bed; red = CTV boost. . (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

well as to feed the models for auto-segmentation with high-quality data.

2.2. Automated treatment planning

Radiation treatment planning is based on a specified dose prescription per target volume coverage and constraints for the OARs. Overall, computer software algorithms are used to optimise dose distributions based on predefined set-up techniques (like scripts) mixed with treatment planner's expertise, often leading to a compromise between targets coverage and OARs sparing. This process of RT planning is time-consuming due to a significant number of manual steps and numerous iterations that are necessary for dosimetric optimisation. It involves RTTs, dosimetrists, medical physicists, and physicians [40]. A lack of uniform working procedures exists within different tumour sites. Therefore, significant gains in time and quality could be obtained by using standardised procedures and scripts.

Recently, AI-based technology was introduced for automated treatment planning [41–45], showing very promising clinical applications for several treatment sites and technical modalities. Mathematical algorithms for knowledge-based treatment planning and quality assurance with few manual interventions were applied [46–48] to predict achievable dose distributions for an individual patient's anatomy and dose prescription based on a database of high-quality treatment plans. Several ML methods, including support vector regression with principal component analysis, voxel-wise dose prediction/optimisation, and knowledge-based isodoses manipulation, were used to create optimised dose distributions [42,46,49].

The use of AI for breast cancer treatment planning using automated treatment planning methodology for intensity modulated radiation therapy (IMRT) was evaluated at the Princess Margaret Hospital [50,51]. The authors showed an increase in clinical acceptance, and an improved quality and efficiency as compared to the current treatment planning process, allowing faster adoption of modern treatment for breast cancer patients. Promising results for treatment planning of the breast combined with the nodal regions are obtained using volumetric modulated arc therapy (VMAT) [52]. The authors obtained a good quality of the obtained dose distributions, comparable to manually prepared treatment plans, with substantially shorter total planning times: average 163 ± 97 and 33 ± 5 min for manual and automated plans, respectively, with approximately 130 and 5 min of user interaction. Marrazzo and colleagues used automated treatment planning for patients treated with accelerated partial breast irradiation using VMAT [53]. They observed a statistically significant improvement in PTV coverage compared to manual treatment planning, without a difference in OAR doses.

While AI applications in treatment planning shows very promising first clinical applications, simplifying the optimisation process and sparing time and resources required for treatment planning, expert verification with eventual manual intervention remains needed, as for automated-contouring.

3. Future perspectives: exploiting spatial distribution of breast cancer recurrences

The use of AI to guide treatment prescription primarily consists of assisting in the individualising of the therapeutic approach to every single patient. Models integrating clinical and pathological findings, imaging, treatment, and outcome data were presented more than 5 years ago [54]. Tumour-site dedicated algorithms in combination with modern RT approaches enable to individually adapt dose-volume parameters to the distribution of recurrence risks. For this, the identification of high- and low-risk areas for local (LR) and loco-regional recurrence (LRR) are required. This should be based on a combination of parameters including individual patient-related factors (e.g., age, comorbidity, body habitus, anatomy), disease-related factors (e.g., initial tumour location within the breast, type of surgery, stage, pathology, biomarkers), treatment-related factors (e.g., extent of surgery, systemic treatments). These data should be matched to parameters derived from trial as well as general population *big data* sources.

3.1. Local recurrence

Two fundamental studies that guided the understanding of the distribution of LR were the Milan [55] (n = 701) and the NSABP-06 [56] (n = 1851) trials, both reported at 20-year follow-up data. Mastectomy was compared to breast-conserving surgery (BCS) plus radiation, with the NSABP-06 trial having a third arm of BCS alone [56]. The probability of tumour recurrence was significantly higher in the BCS group (8.5%) as compared to the mastectomy group (2.3%) [55]. Similarly, the LR rates in the NSABP-06 [56] were lowest in the mastectomy group (10.2%, as first event) as compared to BCS-alone (39.2%) and BCS plus RT (14.3%) [56]. In case of BCS, the tumour bed represents the most frequent site recurrences. A later publication from Veronesi's group [57] described the sites of LR in 2784 patients who underwent BCS and RT. These data were supported by several studies showing that in-breast recurrences occur mostly near or at the original tumour site (around 70%) [58–60]. In case of mastectomy, the residual glandular tissue, the skin (T4 stages), and the subdermal lymphatics anterior to the pectoralis muscles are most at risk for LR. A systematic review of surgical series with detailed analysis of chest wall recurrences of 278 patients reported that between 72 and 100% of LR are within the skin and subcutaneous tissues anterior to the pectoral muscles [59,61–66]. Residual breast glandular tissue can be found in a significant number of patients (around 20%) and varies according to the surgical procedure [67,68]. A postmastectomy MRI study reported that up to 50% of the patients who underwent nipple-sparing procedures had residual glandular tissue (most retro-mammillary region) as compared to 13% of the patients who underwent skin-sparing mastectomy (most lateral breast border) [67]. Another postmastectomy MRI study of patients who underwent implant-based breast reconstruction reported more residual tissue in the cranial and caudal directions as compared to medial or lateral [68].

Spatial distribution of recurrences after both BCS and mastectomy mostly concerns high-risk areas (glandular tissue, skin, subcutaneous lymphatics). Less frequently recurrences may occur within the pectoral muscles, intercostal muscles, and ribs [59]. Clinico-pathological predictive factors for recurrences include age, tumour stage, molecular subtype (luminal-A < luminal-B < HER2 positive < triple negative), lymph vascular invasion, ductal carcinoma in situ (DCIS) component, and lymph nodes involvement [55–57,66,69,70]. Treatment-related factors include endocrine therapy in ER-positive, targeted anti-HER2 treatments in HER2 positive, and chemotherapy mostly for triple-negative disease.

3.2. Locoregional recurrence

Chang and colleagues [59,66] elaborated a three-dimensional map to illustrate the distribution of LRR. Axillary lymph node level 4 (formerly called supraclavicular) was the most common recurrence site (33.8% of all lesions), all being located within 6 mm cranial to the subclavian artery. Other regions of axillary lymph nodes failure were in level 1 (28.3%), level 2 (14.3%), and level 3 (8.9%) [59,66]. Most internal mammary node (IMN) relapses occurred in the upper three intercostal spaces [59,66]. The probability of IMN involvement is related to the primary tumour location and the involvement of the axillary nodes [71–74]. Other clinico-pathological predictive factors for LRR include age, nodal tumour burden, molecular subtype, tumour grade, lymph vascular invasion, and extracapsular extension [66,75,76].

3.3. Tissue characterization

Tissue characterization for breast cancer risk assessment is currently being developed based on computer-extracted characteristics of breast density and parenchymal patterns related to breast cancer risk factors. Using radiomic texture analysis, Li et al. [77], found that women at high risk for breast cancer have more dense breasts. Based on this, DL is now being explored to combine data on breast density with parenchymal characterization, relating patterns through a neuronal network architecture to groups of women using surrogate markers of risk [78–80].

In several tumour types, disease genomics and proteomics can be used to predict response to systemic therapy and prognosis. However, tumour genetics data are not currently in use to guide RT. In a recent publication, Scott and colleagues [81] developed a tool for genomic-adjusted radiation dose (GARD), a model to individually adapt the prescription of RT based on a 10-gene expression profile and the linear quadratic model. This algorithm was based on the Radio-Sensitivity Index (RSI) [82]. The authors used the given RT dose considering the RSI and the linear-quadric model to calculate the GARD, and correlated it with the oncological outcomes in relation to the RT doses given. Having tools like the GARD to assist the decision-making regarding the RT dose may lead to significant changes in our treatment approach and outcomes [83].

4. Discussion

The authors do believe that AI in the radiation oncology field could now play a crucial role in predicting recurrences, since nowadays we probably have enough data *to feed* the DL algorithms. Further steps for AI in breast cancer RT planning will be optimising dose distributions to individualise prescription according to the spatial location of LR and LRR, and – in the near future – to tumour genomics (such as the GARD) (Fig. 2). In order to incorporate available data to achieve appropriate coverage of high-risk areas and to de-escalate doses in low-risk areas to avoid potential toxicity, we strongly need fast implementation of DL methods, neuronal network for automatic segmentation, deformable registration, response-adaptive clinical decision-making, refined imaging generation tools, and toxicity prediction models [84–89].

During the last twenty years, few prediction models have been developed and partially validated to personalize non-metastatic breast cancer systemic treatments, including the Adjuvant! Online and PREDICT tools [90–93]. Adjuvant! Online was developed using the Surveillance, Epidemiology and End-Results (SEER) registry to predict the 10-year risks for recurrence, breast cancer specific-mortality and mortality due to other causes, considering the expected benefit of postoperative systemic therapies [90]. PREDICT was developed using cancer registry data from the United Kingdom and predicts 5-year and 10-year overall survival for individual breast cancer patients, providing the expected benefits of chemo-, endocrine- and target-therapy [91,92]. However, these statistical models – where a preconceived structure is imposed on the relationship between predictors and outcomes – cannot be considered AI applications, where – conversely –ML *lets the data speak*.

Moreover, only limited research data about predictive models specifically related to the outcomes of RT for breast cancer patients is available. Van Werkhoven and colleagues [94] developed a nomogram to predict the 10-year LR risks after BCS plus RT without or with a boost to the primary tumour bed based on the data from 1603 patients from the EORTC boost-no-boost trial. The nomogram included seven factors, such as young age, the presence of DCIS, and the omission of a boost as the most important risk-increasing factors (http://research.nki.nl/ibr/©2012, NKI/AvL). It provides a tool to estimate both the risk of ipsilateral breast relapse and the development of moderate or severe fibrosis. It may hereby assist in decision-making for the use of a boost in individual patients based

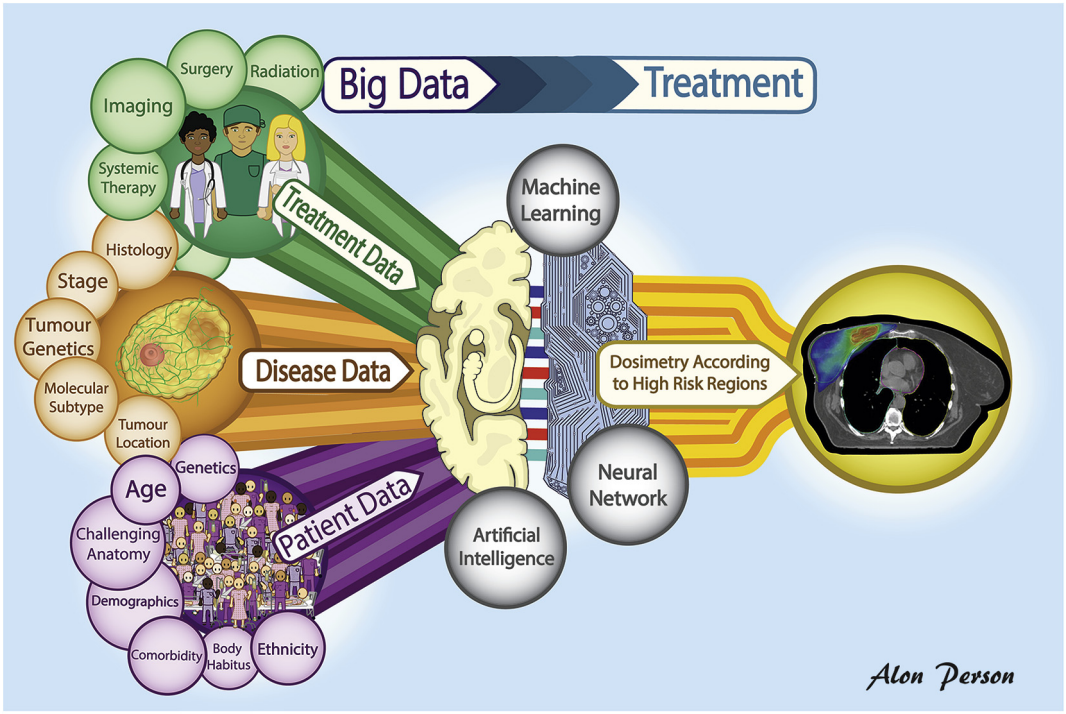

Fig. 2. Artificial Intelligence infographic showing how a large data set containing patient-, tumour- and treatment-related parameters can be processed to optimise risk-adapted radiation therapy dose distributions. Illustration made by Alon Person, using Adobe Illustrator cc 2019.

on the balance between the reduction of LR vs. a higher risk for fibrosis and thereby a less optimal cosmetic results [94].

5. Conclusions

Although the *Winter is over* for applications of AI, ML, and neural networks in the era of *precision medicine* and – particularly – in the field of radiation oncology, we can – at this moment – just talk about an early budding phase of the first trees in spring (Fig. 2). We do not expect that human knowledge and experience will be totally replaced by AI-based applications, that could rather represent an effective supportive tool in diagnosis, treatment planning, and prediction of side effects and outcomes. The optimisation and individualization of dose distributions in treatment planning for breast cancer is just one of the current development directions of these new technologies. The needs for *big data* sources, including detailed data of radiation therapy delivery combined with outcomes, requires collaboration at national and international level to set up large cancer networks sharing both costs and benefits of these exciting new developments.

References

[1] Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA A Cancer J Clin 2018 Nov;68(6):394–424.
[2] Biganzoli L, Marotti L, Hart CD, et al. Quality indicators in breast cancer care: an update from the EUSOMA working group. Eur J Cancer 2017;86:59–81.
[3] Russell S, Bohannon J. Artificial intelligence. Fears of an AI pioneer. Science 2015;349:252.
[4] Buchanan B. A (very) brief history of artificial intelligence. AI Mag 2005;26:8.
[5] Hammond AL. Artificial intelligence: a fascination with robots. Science 1973;180:1352–3.
[6] Schweisheimer W. [Robot machines of diagnosis in the hospitals]. Veska 1962;26:991–2.
[7] Seyhan AA, Carini C. Are innovation and new technologies in precision medicine paving a new era in patients centric care? J Transl Med 2019;17:114.
[8] Simonyan K, Zisserman A. Very deep convolutional networks for large-scale image recognition. Computer Science. 2014. Available from: URL, https://arxiv.org/pdf/1409.1556.pdf.
[9] Girshick R, Donahue J, Darrell T, Malik J. Rich feature hierarchies for accurate object detection and semantic segmentation. Available from: URL, https://arxiv.org/abs/1311.25242014.
[10] Kyono T, Gilbert FJ, van der Schaar M. Improving workflow efficiency for mammography using machine learning. J Am Coll Radiol 2019 May 30. pii: S1546-1440(19)30596-4.
[11] Brouwers P, van Werkhoven E, Bartelink H, et al. Predictors for poor cosmetic outcome in patients with early stage breast cancer treated with breast conserving therapy: results of the Young boost trial. Radiother Oncol 2018;128:434–41.
[12] Joosten A, Matzinger O, Jeanneret-Sozzi W, et al. Evaluation of organ-specific peripheral doses after 2-dimensional, 3-dimensional and hybrid intensity modulated radiation therapy for breast cancer based on Monte Carlo and convolution/superposition algorithms: implications for secondary cancer risk assessment. Radiother Oncol 2013;106:33–41.
[13] Offersen BV, Boersma LJ, Kirkove C, et al. ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer, version 1.1. Radiother Oncol 2016;118:205–8.
[14] Qatarneh SM, Noz ME, Hyodynmaa S, et al. Evaluation of a segmentation procedure to delineate organs for use in construction of a radiation therapy planning atlas. Int J Med Inform 2003;69:39–55.
[15] Gregoire V, Levendag P, Ang KK, et al. CT-based delineation of lymph node levels and related CTVs in the node-negative neck: DAHANCA, EORTC, GORTEC, NCIC,RTOG consensus guidelines. Radiother Oncol 2003;69:227–36.
[16] Sykes J. Reflections on the current status of commercial automated segmentation systems in clinical practice. J Med Radiat Sci 2014;61:131–4.
[17] Thomson D, Boylan C, Liptrot T, et al. Evaluation of an automatic segmentation algorithm for definition of head and neck organs at risk. Radiat Oncol 2014;9:173.
[18] Anders LC, Stieler F, Siebenlist K, et al. Performance of an atlas-based autosegmentation software for delineation of target volumes for radiotherapy of breast and anorectal cancer. Radiother Oncol 2012;102:68–73.
[19] Thompson RF, Valdes G, Fuller CD, et al. Artificial intelligence in radiation oncology: a specialty-wide disruptive transformation? Radiother Oncol 2018;129:421–6.
[20] Meyer P, Noblet V, Mazzara C, et al. Survey on deep learning for radiotherapy. Comput Biol Med 2018;98:126–46.
[21] Boon IS, Au Yong T, Boon CS. Assessing the role of artificial intelligence (AI) in clinical oncology: utility of machine learning in radiotherapy target volume delineation. Medicine (Basel) 2018 Dec 11;5(4). pii: E131.
[22] Xu H, Arsene Henry A, Robillard M, et al. The use of new delineation tool "MIRADA" at the level of regional lymph nodes, step-by-step development and first results for early-stage breast cancer patients. Br J Radiol 2018;91:

20180095.
[23] Sharp G, Fritscher KD, Pekar V, et al. Vision 20/20: perspectives on automated image segmentation for radiotherapy. Med Phys 2014;41:050902.
[24] Walker GV, Awan M, Tao R, et al. Prospective randomized double-blind study of atlas-based organ-at-risk autosegmentation-assisted radiation planning in head and neck cancer. Radiother Oncol 2014;112:321–5.
[25] Lim JY, Leech M. Use of auto-segmentation in the delineation of target volumes and organs at risk in head and neck. Acta Oncol 2016;55:799–806.
[26] Cardenas CE, McCarroll RE, Court LE, et al. Deep learning algorithm for auto-delineation of high-risk oropharyngeal clinical target volumes with built-in dice similarity coefficient parameter optimization function. Int J Radiat Oncol Biol Phys 2018;101:468–78.
[27] Li Q, Xu Y, Chen Z, et al. Tumor segmentation in contrast-enhanced magnetic resonance imaging for nasopharyngeal carcinoma: deep learning with convolutional neural network. BioMed Res Int 2018;2018:9128527.
[28] Lustberg T, van Soest J, Gooding M, et al. Clinical evaluation of atlas and deep learning based automatic contouring for lung cancer. Radiother Oncol 2018;126:312–7.
[29] Martin S, Rodrigues G, Patil N, et al. A multiphase validation of atlas-based automatic and semiautomatic segmentation strategies for prostate MRI. Int J Radiat Oncol Biol Phys 2013;85:95–100.
[30] Dipasquale G, Wang X, Chatelain-Fontanella V, et al. Automatic segmentation of breast in prone position: correlation of similarity indexes and breast pendulousness with dose/volume parameters. Radiother Oncol 2016;120:124–7.
[31] Eldesoky AR, Yates ES, Nyeng TB, et al. Internal and external validation of an ESTRO delineation guideline - dependent automated segmentation tool for loco-regional radiation therapy of early breast cancer. Radiother Oncol 2016;121:424–30.
[32] Men K, Zhang T, Chen X, et al. Fully automatic and robust segmentation of the clinical target volume for radiotherapy of breast cancer using big data and deep learning. Phys Med 2018;50:13–9.
[33] Reed VK, Woodward WA, Zhang L, et al. Automatic segmentation of whole breast using atlas approach and deformable image registration. Int J Radiat Oncol Biol Phys 2009;73:1493–500.
[34] Ciardo D, Gerardi MA, Vigorito S, et al. Atlas-based segmentation in breast cancer radiotherapy: evaluation of specific and generic-purpose atlases. Breast 2017;32:44–52.
[35] Eriksen JG, Salembier C, Rivera S, et al. Four years with FALCON - an ESTRO educational project: achievements and perspectives. Radiother Oncol 2014;112:145–9.
[36] Offersen BV, Boersma LJ, Kirkove C, et al. ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer. Radiother Oncol 2015;114:3–10.
[37] White JT, Arthur D, Buchholz T, et al. Breast cancer atlas for radiation therapy planning: consensus definitions. Available from: URL, http://www.rtog.org/LinkClick. aspx?fileticketZvzJFhPaBipEZ. [Accessed 21 February 2017].
[38] Kaidar-Person O, Vrou Offersen B, Hol S, et al. ESTRO ACROP consensus guideline for target volume delineation in the setting of postmastectomy radiation therapy after implant-based immediate reconstruction for early stage breast cancer. Radiother Oncol 2019;137:159–66.
[39] Mak RH, Endres MG, Paik JH, et al. Use of crowd innovation to develop an artificial intelligence-based solution for radiation therapy targeting. JAMA Oncol 2019 May 1;5(5):654–61.
[40] McIntosh C, Welch M, McNiven A, et al. Fully automated treatment planning for head and neck radiotherapy using a voxel-based dose prediction and dose mimicking method. Phys Med Biol 2017;62:5926–44.
[41] Kearney V, Chan JW, Valdes G, et al. The application of artificial intelligence in the IMRT planning process for head and neck cancer. Oral Oncol 2018;87:111–6.
[42] Campbell WG, Miften M, Olsen L, et al. Neural network dose models for knowledge-based planning in pancreatic SBRT. Med Phys 2017;44:6148–58.
[43] Schubert C, Waletzko O, Weiss C, et al. Intercenter validation of a knowledge based model for automated planning of volumetric modulated arc therapy for prostate cancer. The experience of the German RapidPlan Consortium. PLoS One 2017;12:e0178034.
[44] Nwankwo O, Mekdash H, Sihono DS, et al. Knowledge-based radiation therapy (KBRT) treatment planning versus planning by experts: validation of a KBRT algorithm for prostate cancer treatment planning. Radiat Oncol 2015;10:111.
[45] Huang Y, Li S, Yue H, et al. Impact of nominal photon energies on normal tissue sparing in knowledge-based radiotherapy treatment planning for rectal cancer patients. PLoS One 2019;14:e0213271.
[46] Zhu X, Ge Y, Li T, et al. A planning quality evaluation tool for prostate adaptive IMRT based on machine learning. Med Phys 2011;38:719–26.
[47] Nwankwo O, Sihono DS, Schneider F, et al. A global quality assurance system for personalized radiation therapy treatment planning for the prostate (or other sites). Phys Med Biol 2014;59:5575–91.
[48] Sheng Y, Ge Y, Yuan L, et al. Outlier identification in radiation therapy knowledge-based planning: a study of pelvic cases. Med Phys 2017;44:5617–26.
[49] Shiraishi S, Moore KL. Knowledge-based prediction of three-dimensional dose distributions for external beam radiotherapy. Med Phys 2016;43:378.
[50] Purdie TG, Dinniwell RE, Letourneau D, et al. Automated planning of tangential breast intensity-modulated radiotherapy using heuristic optimization. Int J Radiat Oncol Biol Phys 2011;81:575–83.
[51] Purdie TG, Dinniwell RE, Fyles A, et al. Automation and intensity modulated radiation therapy for individualized high-quality tangent breast treatment plans. Int J Radiat Oncol Biol Phys 2014;90:688–95.
[52] van Duren-Koopman MJ, Tol JP, Dahele M, et al. Personalized automated treatment planning for breast plus locoregional lymph nodes using Hybrid RapidArc. Pract Radiat Oncol 2018;8:332–41.
[53] Marrazzo L, Meattini I, Arilli C, et al. Auto-planning for VMAT accelerated partial breast irradiation. Radiother Oncol 2019;132:85–92.
[54] Lambin P, Roelofs E, Reymen B, et al. Rapid Learning health care in oncology' - an approach towards decision support systems enabling customised radiotherapy. Radiother Oncol 2013;109:159–64.
[55] Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med 2002;347:1227–32.
[56] Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 2002;347:1233–41.
[57] Botteri E, Bagnardi V, Rotmensz N, et al. Analysis of local and regional recurrences in breast cancer after conservative surgery. Ann Oncol 2010;21:723–8.
[58] Luini A, Gatti G, Zurrida S, et al. The evolution of the conservative approach to breast cancer. Breast 2007;16:120–9.
[59] Chang JS, Byun HK, Kim JW, et al. Three-dimensional analysis of patterns of locoregional recurrence after treatment in breast cancer patients: validation of the ESTRO consensus guideline on target volume. Radiother Oncol 2017;122:24–9.
[60] Fowble B, Solin LJ, Schultz DJ, et al. Breast recurrence following conservative surgery and radiation: patterns of failure, prognosis, and pathologic findings from mastectomy specimens with implications for treatment. Int J Radiat Oncol Biol Phys 1990;19:833–42.
[61] Vargo JA, Beriwal S. RTOG chest wall contouring guidelines for post-mastectomy radiation therapy: is it evidence-based? Int J Radiat Oncol Biol Phys 2015;93:266–7.
[62] Slavin SA, Love SM, Goldwyn RM. Recurrent breast cancer following immediate reconstruction with myocutaneous flaps. Plast Reconstr Surg 1994;93:1191–204. discussion 205-7.
[63] Donegan WL, Perez-Mesa CM, Watson FR. A biostatistical study of locally recurrent breast carcinoma. Surg Gynecol Obstet 1966;122:529–40.
[64] Noone RB, Frazier TG, Noone GC, et al. Recurrence of breast carcinoma following immediate reconstruction: a 13-year review. Plast Reconstr Surg 1994;93:96–106. discussion 7-8.
[65] Langstein HN, Cheng MH, Singletary SE, et al. Breast cancer recurrence after immediate reconstruction: patterns and significance. Plast Reconstr Surg 2003;111:712–20. discussion 21-2.
[66] Chang JS, Lee J, Chun M, et al. Mapping patterns of locoregional recurrence following contemporary treatment with radiation therapy for breast cancer: a multi-institutional validation study of the ESTRO consensus guideline on clinical target volume. Radiother Oncol 2018;126:139–47.
[67] Woitek R, Pfeiler G, Farr A, et al. MRI-based quantification of residual fibroglandular tissue of the breast after conservative mastectomies. Eur J Radiol 2018;104:1–7.
[68] Zippel D, Tsehmaister-Abitbol V, Rundstein A, et al. Magnetic resonance imaging (MRI) evaluation of residual breast tissue following mastectomy and reconstruction with silicone implants. Clin Imaging 2015;39:408–11.
[69] Vrieling C, van Werkhoven E, Maingon P, et al. Prognostic factors for local control in breast cancer after long-term follow-up in the EORTC boost vs No boost trial: a randomized clinical trial. JAMA Oncol 2017 Jan 1;3(1):42–8.
[70] Vrieling C, van Werkhoven E, Maingon P, et al. Prognostic factors for local control in breast cancer after long-term follow-up in the EORTC boost vs No boost trial: a randomized clinical trial. JAMA Oncol 2017;3:42–8.
[71] van der Ent FW, Kengen RA, van der Pol HA, et al. Halsted revisited: internal mammary sentinel lymph node biopsy in breast cancer. Ann Surg 2001;234:79–84.
[72] Estourgie SH, Tanis PJ, Nieweg OE, et al. Should the hunt for internal mammary chain sentinel nodes begin? An evaluation of 150 breast cancer patients. Ann Surg Oncol 2003;10:935–41.
[73] Estourgie SH, Nieweg OE, Olmos RA, et al. Lymphatic drainage patterns from the breast. Ann Surg 2004;239:232–7.
[74] Vendrell-Torne E, Setoain-Quinquer J, Domenech-Torne FM. Study of normal mammary lymphatic drainage using radioactive isotopes. J Nucl Med 1972;13:801–5.
[75] DeSelm CJY TJ, Tisnado J, Wilgucki M, Pei X, Siu CT, McCormick B, Cahlon O, Powell SN, Ho AY. Regional patterns of breast cancer failure after definitive therapy: a large, single-institution analysis. Int J Radiat Oncol Biol Phys 2016;96:S145.
[76] Reed VK, Cavalcanti JL, Strom EA, et al. Risk of subclinical micrometastatic disease in the supraclavicular nodal bed according to the anatomic distribution in patients with advanced breast cancer. Int J Radiat Oncol Biol Phys 2008;71:435–40.
[77] Li H, Giger ML, Lan L, et al. Computerized analysis of mammographic parenchymal patterns on a large clinical dataset of full-field digital mammograms: robustness study with two high-risk datasets. J Digit Imaging 2012;25:591–8.
[78] Li S, Wei J, Chan HP, et al. Computer-aided assessment of breast density:

comparison of supervised deep learning and feature-based statistical learning. Phys Med Biol 2018;63:025005.
[79] Lee J, Nishikawa RM. Automated mammographic breast density estimation using a fully convolutional network. Med Phys 2018;45:1178–90.
[80] Li H, Giger ML, Huynh BQ, et al. Deep learning in breast cancer risk assessment: evaluation of convolutional neural networks on a clinical dataset of full-field digital mammograms. J Med Imaging 2017;4:041304.
[81] Scott JG, Berglund A, Schell MJ, et al. A genome-based model for adjusting radiotherapy dose (GARD): a retrospective, cohort-based study. Lancet Oncol 2017;18:202–11.
[82] Eschrich S, Zhang H, Zhao H, et al. Systems biology modeling of the radiation sensitivity network: a biomarker discovery platform. Int J Radiat Oncol Biol Phys 2009;75:497–505.
[83] Poortmans P, Kaidar-Person O, Span P. Radiation oncology enters the era of individualised medicine. Lancet Oncol 2017;18:159–60.
[84] Esteva A, Kuprel B, Novoa RA, et al. Dermatologist-level classification of skin cancer with deep neural networks. Nature 2017;542:115–8.
[85] Men K, Dai J, Li Y. Automatic segmentation of the clinical target volume and organs at risk in the planning CT for rectal cancer using deep dilated convolutional neural networks. Med Phys 2017;44:6377–89.
[86] Neylon J, Min Y, Low DA, et al. A neural network approach for fast, automated quantification of DIR performance. Med Phys 2017;44:4126–38.
[87] Tseng HH, Luo Y, Cui S, et al. Deep reinforcement learning for automated radiation adaptation in lung cancer. Med Phys 2017;44:6690–705.
[88] Han X. MR-based synthetic CT generation using a deep convolutional neural network method. Med Phys 2017;44:1408–19.
[89] Zhen X, Chen J, Zhong Z, et al. Deep convolutional neural network with transfer learning for rectum toxicity prediction in cervical cancer radiotherapy: a feasibility study. Phys Med Biol 2017;62:8246–63.
[90] Ravdin PM, Siminoff LA, Davis GJ, et al. Computer program to assist in making decisions about adjuvant therapy for women with early breast cancer. J Clin Oncol 2001;19:980–91.
[91] Wishart GC, Azzato EM, Greenberg DC, et al. PREDICT: a new UK prognostic model that predicts survival following surgery for invasive breast cancer. Breast Cancer Res 2010;12:R1.
[92] Candido Dos Reis FJ, Wishart GC, Dicks EM, et al. An updated PREDICT breast cancer prognostication and treatment benefit prediction model with independent validation. Breast Cancer Res 2017;19:58.
[93] van Maaren MC, van Steenbeek CD, Pharoah PDP, et al. Validation of the online prediction tool PREDICT v. 2.0 in the Dutch breast cancer population. Eur J Cancer 2017;86:364–72.
[94] van Werkhoven E, Hart G, Tinteren H, et al. Nomogram to predict ipsilateral breast relapse based on pathology review from the EORTC 22881-10882 boost versus no boost trial. Radiother Oncol 2011;100:101–7.