Possible Role of Adjuvant rapid arc radiotherapy in Breast Cancer Treatment

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Abstract

Breast cancer is the leading diagnosed cancer and the second most common cause of cancer mortality in sub-Saharan Africa. RapidArc has been employed for tumors in several other parts of the body, eg, in breast canceThere are two main forms of arc-based therapies: tomotherapy and volumetric modulated arc therapy (VMAT). Tomotherapy (i.e. “slice therapy”) machines can be considered to be a combination of a CT scanner and a linear accelerator that can deliver the radiation in a fan-shaped distribution, similar to CT imaging with a continuously rotating radiation source, while the patient is moved through the machine. Tomotherapy techniques can be subdivided into axial or serial tomotherapy (where the radiation is delivered slice by slice) or helical tomotherapy (HT) (where the radiation is delivered in a continuous spiral). There is limited data on axial tomotherapy in comparison with fixed field IMRT. HT has been evaluated in a variety of tumour sites and it can generally achieve either similar or improved dose distributions compared with fixed field IMRT, with variable results on treatment time comparisonsr. In these studies, it was a common finding that RapidArc was more efficient for dose delivery, while with regard to treatment planning and dose conformity, RapidArc provided considerable added value. These studies emphasize that RapidArc and, in wider terms, VMAT techniques can be considered a possible alternative to traditional irradiation methods for the cure of several cancers

Keywords: Adjuvant rapid arc, radiotherapy, Breast Cancer

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Introduction

Breast cancer is the leading diagnosed cancer and the second most common cause of cancer mortality in sub-Saharan Africa [1]. Sub-Saharan Africa has the highest age-standardized incidence rate of 17.3 per 100,000 women per year, globally; with the Southern Africa region and West African region having the highest age-standardized incidence rate of 38.9 and 38.6 per

100,000 women per year in sub-Saharan Africa, respectively. However, the Northern Africa region has the highest incidence rate of 43.2 ASR incidence in the whole of Africa [1].

Country-specific prevalence shows that there is a 15.3%, 4.6% and 3.3% prevalence of breast cancer in the Central African Republic, Rwanda and Sierra Leone, respectively. Mauritius and Nigeria have been said to be the countries with the highest incidence in Africa at 64.2 and 50.4 ASR incidence per 100,000 repetitively [2].

African trends on breast cancer

Some of the most rapid increases are occurring in sub-Saharan Africa. Between the mid-1990s and the mid-2010s, incidence rates increased by >5% per year in Malawi (Blantyre), Nigeria (Ibadan), and Seychelles and by 3% to 4% per year in South Africa (Eastern Cape and Zimbabwe (Harare) [3]. Between 2008 and 2012, East Africa experienced the largest incidence rate increase of 36.5% from 19.30 ASR in 2008 incidence to 30.4 ASR in 2012. However, the incidence remains highest in the North African region at 43.2 ASR; with southern Africa having the lowest increase of 2% from 38.2 ASR incidence in 2008 to 38.9 ASR incidence in 2012 [3].

In southern Ethiopia, there has been an increasing incidence of breast cancer between 2013 and 2019 according to institutional records. It has increased from 12.3% in 2013 to 19.0% in 2019. Nigeria has continuously shown increases in incident rates from 13.7 ASR between 1960 and 1969 to 50.4 ASR between 2000 and 2012 and has been projected to 84.2 ASR between 2013 and 2050. In Central African Republic, the average prevalence rate has been on the increase; with breast cancer prevalence just above 10% in 2003 and just above 15% in 2015 among breast cancer patients; after dropping from 20% in 2014 [4].

Despite the difference in incidence rates of BC between developed and developing countries, the disease remains the most common type of female cancer in Egypt with an age-specific incidence rate of 48.8/105. Approximately 46,000 incident cases are forecasted in 2050. Although this incidence rate in Egypt is lower than the global figures, mortality is higher at an age-standardized rate of 20.4/100,000 compared with the US rate of 12.3/105 and the developed countries' rate of 12.8/10. [5] When comparing the mortality/incidence rate ratio for BC between Egypt and developed countries, Egypt had approximately double the ratio (41% v 23%). Moreover, it is currently the second most common cause of Egyptian cancer mortality after hepatocellular carcinoma with estimated mortality rate around 11% in 2020. Notably, this mortality rate is far higher than those of other developing countries counterparts like China, where age-standardized mortality rate is 6.3/105. [6]

There are two main forms of arc-based therapies: tomotherapy and volumetric modulated arc therapy (VMAT). Tomotherapy (i.e. “slice therapy”) machines can be considered to be a combination of a CT scanner and a linear accelerator that can deliver the radiation in a fan-shaped distribution, similar to CT imaging with a continuously rotating radiation source, while the patient is moved through the machine. Tomotherapy techniques can be subdivided into axial or serial tomotherapy (where the radiation is delivered slice by slice) or helical tomotherapy (HT) (where the radiation is delivered in a continuous spiral). There is limited data on axial tomotherapy in comparison with fixed field IMRT. HT has been evaluated in a variety of

tumour sites and it can generally achieve either similar or improved dose distributions compared with fixed field IMRT, with variable results on treatment time comparisons [7].

VMAT was first introduced in 2007 and described as a novel radiation technique that allowed the simultaneous variation of three parameters during treatment delivery, i.e. gantry rotation speed, treatment aperture shape via movement of MLC leaves and dose rate [8]. The earlier form of arc therapy, termed intensity modulated arc therapy (IMAT) was first described in 1995 and required the use of multiple superimposed arcs to achieve a satisfactory dose distribution. More recent VMAT techniques have allowed the whole target volume to be treated using one or two arcs, although complex cases may require more. In a recent review, VMAT is essentially described as a form of single arc IMAT technique that employs dose rate variation [9].

One benefit of VMAT compared with tomotherapy is the possibility of delivering this treatment on conventional linear accelerators, which are configured to have this capability. Currently there are several VMAT systems available under various names (RapidArc, Varian; SmartArc, Phillips; and Elekta VMAT, Elekta) [10].

Varian Medical Systems, Inc. (Palo alto, CA, USA) has launched into the marketplace a new arc delivery technique named RapidArc™. In this method, the treatment is delivered in one or more arc rotations of the linac gantry; in this rotation, the multileaf collimators (MLCs) are moving dynamically and, at the same time, the dose rate is varied throughout variation of the gantry speed rotation [11].

The earliest form of arc therapy, termed intensity-modulated arc therapy (IMAT), was first described by Yu et al in 1995 and required the use of multiple superimposed arcs to achieve a satisfactory dose distribution. The general IMAT concept as described by Yu et al makes use of several arcs, all delivered in a cone-beam fashion, but as an “arc-in-arc” approach, where each arc patches in the missing dose levels from the previous arcs to obtain the desired dose distribution [12].

With the RapidArc technique, to obtain an extremely conformal dose distribution by means of the increase of degrees of freedom, the variation of dose rate is gained in a single arc by the mishmash of gantry speed combined with dynamic MLCs, all specified in a large number of control points over the rotation. There is a limit to the modulation factor that is related to the movement allowable of the MLCs per second per degree of gantry rotation. The RapidArc approach can be considered an extension to dynamic MLC IMRT, and the machine commissioning and quality assurance should validate standard dynamic MLC delivery, and the combination with dose rate variations and gantry rotation with variable speed, which is specific to RapidArc [13].

Comparisons between RapidArc and IMRT have been evaluated for quite a lot of tumor sites. Relevant works have largely demonstrated that RapidArc, compared to IMRT, is capable of creating analogous or better dose distributions, compared to IMRT, is capable of creating analogous or better dose distributions, while attaining a reduction in treatment time and monitor units are halved. The quantity of radiation generated by the linear accelerator is expressed in MUs; growth in MUs is connected with a higher scatter radiation from the accelerator, which would hypothetically increase the risk of secondary malignancies. Above all, two studies have

assessed treatment with RapidArc for head and neck cancer and observed that the distribution is comparable to or improved with respect to IMRT; there is a decrease in MUs and, consequently, an important decrease in treatment times [14].

Compared to other techniques, specifically tomotherapy and fixed-field IMRT, RapidArc has the extra benefit of more rapid treatment times. Elongated treatment time has been known as one of the disadvantages of the fixed-field IMRT technique. In the event that the IMRT plan is particularly complicated, the delivery of a fraction of the treatment can last even more than 15–30 minutes; however, most fractions of three-dimensional conformal radiation therapy (3D-CRT) require only a few minutes, depending on difficulty. This has always been considered as an inevitable consequence to achieve an extremely conformal radiotherapy, a condition that we could accept to enhance dose distribution obtained by IMRT [15]. The extension of treatment time has more than a few undesirable implications. It requires patients to pass a lot of time on the radiotherapy couch, which can lead to patient distress and increases the risk of intra-fraction movement of the tumor or patient. Formally, it considerably reduces the quantity of patients who can be treated per treatment unit every day. This is particularly true when considering that the tumors are treated on a slice by-slice basis, as an axial tumor shift could cause a portion of the tumor to be underdosed, notably when single or few large fractions are used [16].

Longer treatment times could cause a following increase of the time needed by the physicians for quality assurance in order to verify the dose distribution before delivering it to the patient. As well, other reflections with prolonged treatment time are necessary, such as there may be detrimental radiobiological consequences. According to some authors, with long treatment times, the tumor cells will have the possibility for DNA repair, leading to their proliferation, as in vitro data from several investigators showed [17].

Particularly demanding radiotherapy treatments, such as stereotactic lung radiotherapy treatments, which are mainly challenging in that they deliver up to 20 Gy per fraction to a moving target, often require 30–45 minutes to deliver radiotherapy treatment utilizing IMRT, whereas, using RapidArc, it can be delivered in 4–11 minutes. The better treatment times with RapidArc are a consequence of a number of factors: more MUs are required for IMRT plans, and this involves having the treatment machine turned on for an extended time, verify and set accurately the parameters field and rotate the gantry require more time to send information to the treatment machine [18]. With RapidArc, the arc must be able to be considered as a single field and all parameters are set just once per arc. Table 1 summarizes some articles relating to treatment times for RapidArc and VMAT techniques and tomotherapy. Figure 1 shows the dose distribution across the most representative RapidArc plans [13].

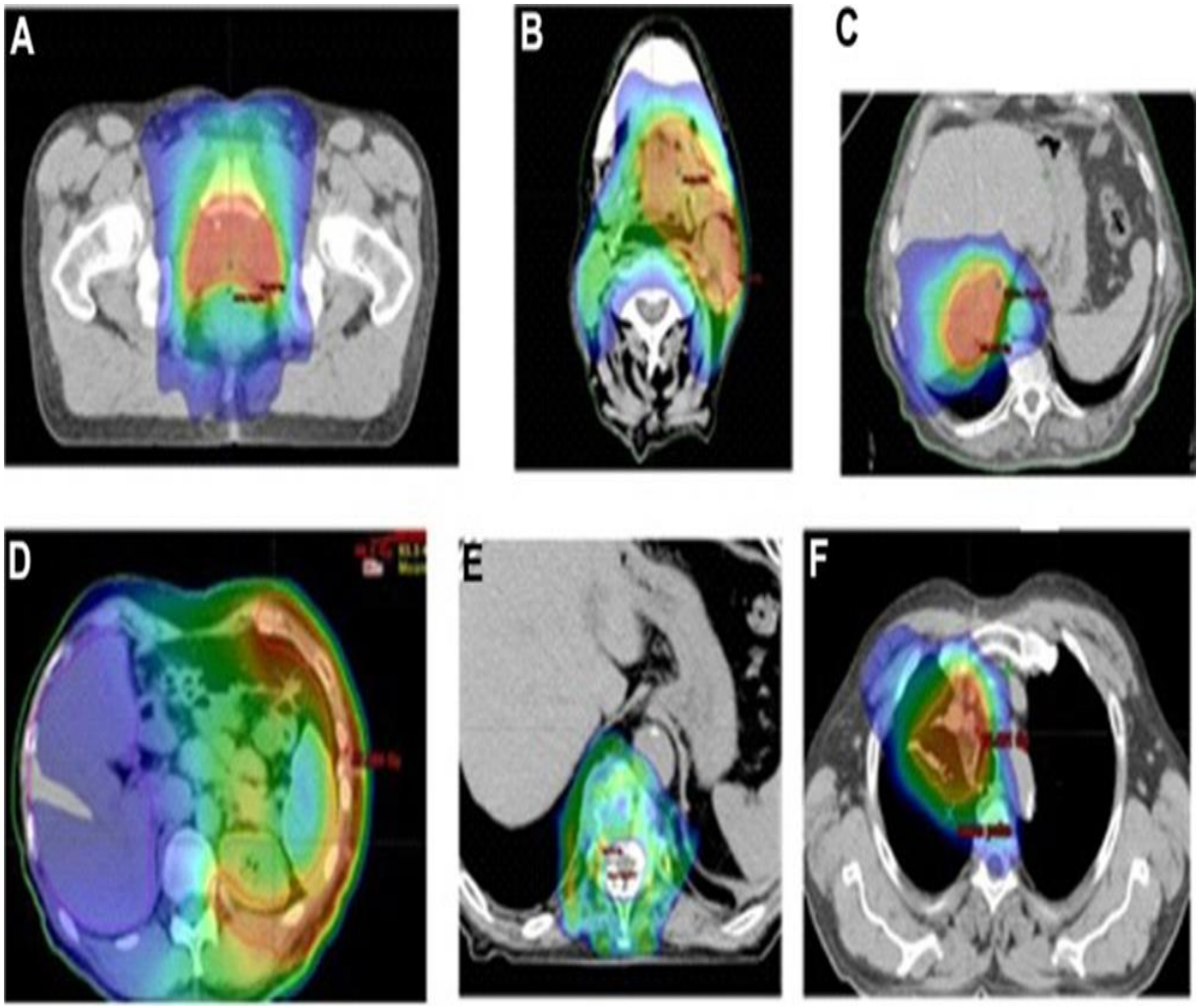

Figure 1 The dose distribution of representative volumetric modulated arc therapy plans. Notes: (A) VMAT plans for radiotherapy to prostate; (B) VMAT plans for oropharyngeal cancer; (C) VMAT plans for radiotherapy to hepatic cancer; (D) VMAT plans for pleural mesothelioma; (E) VMAT plans for spinal cord; (F) VMAT plans for abdominal tumors [13].

Table 1 Representative treatment times with VMAT techniques and tomotherapy [13].

Treatment sites	Dose per fraction	Modalities reported	Treatment times in minutes (mean/range)[a]
Conventionally fractionated treatments			
Several sites	Various	Tomotherapy	6
	Various	Tomotherapy	11
	Various	Tomotherapy	10.7
Several sites – pediatric	Various	Tomotherapy	4.9
Lung	Not specified	VMAT (Elekta)	1.7

Nasopharynx	1.8 Gy	Tomotherapy	8
		IMRT	14
Naso-, oro-, hypopharynx	2 Gy	RapidArc™	1.3–3
		IMRT	8–12
Prostate	Up to 2.65 Gy	Tomotherapy	4–6
	Up to 2.4 Gy	VMAT	3.7
Hypofractionated stereotactic treatments			
Lung	7.5–18 Gy	RapidArc™	4.5–11
		3D-CRT	11–13
Vestibular schwannomas	12.5 Gy	RapidArc™	4–5
Liver and lung	Not specified	Tomotherapy	46
Liver, lung, and spine	5–20 Gy	Tomotherapy (helical and serial)	22–48

Notes: Treatment times may not be directly comparable across studies due to variations in plan complexity. aExcludes time for patient setup or imaging. Abbreviations: 3D-CRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiation therapy; VMAT, volumetric modulated arc therapy.

Breast cancer

RapidArc has been employed for tumors in several other parts of the body, eg, in breast cancer. In these studies, it was a common finding that RapidArc was more efficient for dose delivery, while with regard to treatment planning and dose conformity, RapidArc provided considerable added value. These studies emphasize that RapidArc and, in wider terms, VMAT techniques can be considered a possible alternative to traditional irradiation methods for the cure of several cancers [19].

VMAT has been investigated in a number of different scenarios. Qiu et al conducted a planning study for partial breast radiotherapy in eight patients comparing conventional CRT using four to five non-coplanar fields with VMAT using a modified partial arc. The results showed similar target volume coverage; VMAT had slightly better conformity, although this was not statistically significant. The doses to the ipsilateral lung and ipsilateral normal breast tissue were significantly reduced with VMAT. V20 Gy for the ipsilateral lung was 0.5% in VMAT plans compared with

1.6% in CRT plans while V5 Gy for the ipsilateral breast was 59.6% and 70% for the VMAT and CRT plans, respectively. VMAT also used fewer MU and reduced treatment time compared with conventional radiotherapy. Although partial breast radiotherapy is increasingly considered acceptable for selected patients, this strategy is still not widely used outside of clinical trials and longer follow-up of these patients is needed to assess the long term clinical outcomes. Radiotherapy to the whole breast and/or regional lymph nodes remains the gold standard [20].

The irradiation of internal mammary lymph nodes is not considered standard practice in the UK, but it is performed for selected patients with high risk breast cancer at several institutions worldwide. Conventionally this is done using the modified wide tangent (MWT) technique, which increases the volume of normal tissue (particularly lung and heart) receiving radiation. Popescu et al evaluated VMAT against the conventional MWT technique and nine-field fixed field IMRT (SW) in a group of patients with left-sided breast cancer who also received radiotherapy to the internal mammary nodes. They report similar PTV coverage, dose homogeneity and conformity, but improved sparing of OARs with VMAT, particularly for the heart, ipsilateral lung and contralateral breast [21]. Another similar study by Johansen et al found similar PTV coverage, but improved conformity with IMRT (SW) and VMAT compared with conventional techniques and better homogeneity with VMAT. In their study, there was improved sparing of the ipsilateral lung and contralateral breast with VMAT, but no significant differences in cardiac doses. However, only 3 out of the 8 were left-sided tumours, therefore, definite conclusions on cardiac-sparing cannot be made from this study [22].

Another potential area where IMRT techniques could play a useful role is in the treatment of large target volumes where there is risk of increased radiation dose to OARs (e.g. in bilateral breast cancer) or complex-shaped target volumes (e.g. in patients with an unusually shaped chest wall, such as in cases of pectus excavatum). Nicolini et al conducted a planning study in 10 patients treated for bilateral breast cancer with an SIB technique comparing VMAT and fixed field IMRT (SW). Similar target coverage was found with better dose homogeneity with VMAT. The doses to the heart were lower with VMAT while for the lungs VMAT achieved better sparing at the mid- to high-dose levels (e.g. V20 Gy right lung 10.3% (VMAT) vs 14.5% (IMRT)) compared with IMRT, which gave better sparing at low dose levels (e.g.V5 Gy right lung 58.3% (VMAT) vs 44.4% (IMRT)). The mean and integral dose to healthy tissue was higher with VMAT in this study [16]. In Popescu et al's study, the mean dose to healthy tissue was lower with VMAT, but V5 Gy for healthy tissue was higher, which is consistent with inferior sparing at low dose levels. Another important factor in this patient cohort is the effect of intrafraction motion, which could lead to increased doses to OARs. Although the shorter treatment time with VMAT could reduce the impact of motion, other methods to account for this (e.g. breath-hold or target tracking techniques) should also be considered [21].

The increase in low dose radiation to healthy tissues with IMRT techniques is a concern in this patient cohort. Breast cancer mortality is decreasing owing to a combination of factors including earlier diagnosis via screening and improvements in therapy. Many patients now survive for many years after diagnosis and treatment for breast cancer. It is therefore important to minimise late side effects that could arise from their treatment. Apart from cardiovascular disease, secondary malignancy is a significant cause of non-breast cancer mortality in long-term survivors [23].

The increased risk of secondary malignancy secondary to low dose radiation is currently not accurately quantifiable but should be borne in mind when deciding on the treatment strategy or radiation technique for these patients. IMRT will still play an important role in breast radiotherapy, particularly within the setting of partial breast dose escalation for high-risk disease, which is currently being investigated in the IMPORT-HIGH trial [24].

IMRT techniques can be refined to minimise the amount of low dose radiation to healthy tissues e.g. by setting dose constraints on additional normal tissue structures in the optimisation process or, in the case of VMAT, using partial arcs. While inverse planned IMRT is necessary for complex target volumes, simpler forward planned techniques using multiple segmented tangential fields may be able to produce acceptable dose distributions for less complex cases while also minimising low dose radiation to surrounding normal tissue. As with other tumour sites, it may be that there is no universal optimal solution and the selection of the most appropriate radiation technique, be it conventional CRT, IMRT or VMAT, must be made on an individual case basis [10].

No Conflict of interest.

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