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ORIGINAL ARTICLE

Comparison of the effects of two types of multileaf collimators on tumor control probability in radiotherapy for breast cancer after conservative surgery based on the EUD model*

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Abstract

Objective To compute and compare the tumor control probability (TCP) of volumetric modulated arc therapy (VMAT) for breast cancer after conservative surgery based on two types of multileaf collimator (MLC) through a retrospective planning study.

Methods For a group of 9 patients diagnosed with left breast cancer, VMAT plan based on Agility MLC and beam modulator (BM) MLC were designed. The prescription dose was 50 Gy covering at least 95% of the planning target volume, 2 Gy per fraction. TCPs were calculated according to dose-volume histogram (DVH) analysis.

Results The TCP of the BM VMAT plan was slightly higher than that of the Agility VMAT plan (94.61% vs 94.23%) but was inferior with respect to delivery efficiency; the delivery time was reduced for Agility VMAT plan by 35% compared to BM VMAT plan.

Conclusion For breast cancer radiation therapy after conservative surgery, BM VMAT plans provide slightly higher TCP while the delivery of Agility VMAT plans is significantly faster than the BM VMAT plans.

Key words: tumor control probability (TCP); breast cancer; radiobiology; volumetric modulated arc therapy (VMAT)

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Breast-conserving surgery (BCS) with subsequent whole breast irradiation (WBI) is an effective adjuvant treatment mode for early stage breast cancer. Some long-term clinical trials have shown comparable overall survival and disease-free survival rates for conservative surgery combined with WBI compared with postoperative mastectomy [1–3]. In recent years, volumetric modulated arc therapy (VMAT) has been introduced into clinical practice. VMAT can achieve a higher degree of intensity modulation than conventional intensity modulated radiotherapy (IMRT) by changing the gantry rotation speed, dose rate, and multileaf collimator (MLC) speed simultaneously. Many studies have shown that the VMAT technique may produce better target dose distributions as well as better organs at risk (OARs) sparing than conventional IMRT or three-dimensional conformal radiotherapy (3DCRT) [4–14].

To the best of our knowledge, no comparative studies of the radiobiological effects of different types of MLC on VMAT planning for breast cancer post conservative surgery have been conducted. This study investigated the effect of different MLCs on tumor control probability (TCP) in treating breast cancer with VMAT by comparing treatment plans for 9 patients developed using Elekta Agility and Beam Modulator (BM) (Elekta AB, Sweden).

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Materials and methods

EUD-based TCP radiobiological mathematical model

The equivalent uniform dose (EUD) based radiobiological mathematical model [15] is primarily based on two equations. This mathematical model has an excellent ability in fitting, for example, the Emami *et al*. normal tissue tolerance values [16]. The original definition of the EUD was derived from a mechanistic formulation using a linear quadratic cell survival model [17]. Subsequently, Niemierko *et al* [15] has suggested a phenomenological model of the form:

$$EUD = \left(\sum_{i=1} (v_i D_i^a) \right)^{\frac{1}{a}}$$

Here, a is a dimensionless model parameter that is specific to the tumor and v_i is dimensionless and represents the i'th partial volume receiving dose D_i in Gy. Since the relative volume of the whole structure of interest corresponds to 1, the sum of all partial volumes vi will be equal to 1. The choice of parameter a will determine the behavior of the EUD-based mathematical model. For example, as a increases to a large positive number, the EUD approaches the maximal dose; as a decreases to a large negative number, the EUD approaches the minimal dose; if a is equal to 1, the EUD becomes the dose average; and if a is equal to 0, the EUD is equal to the geometric mean [17]. The local control of a tumor will likely depend on the volume that received the minimum dose, since this is where the tumor cell survival should be highest. Consequently, the EUD for tumors will be close to the minimal dose, and the parameter should be a large negative number.

To calculate the TCP, EUD was calculated in the following equation:

$$TCP = \frac{1}{1 + (\frac{TCD_{50}}{EUD})^{4\lambda 50}} \quad (2)$$

Here, the TCD_{50} is the tumor dose necessary to control 50% of the tumor when the tumor is homogeneously irradiated. $\gamma 50$ is a dimensionless model parameter that is specific to the tumor of interest and describes the slope of the dose response curve. In this study, the parameters for WBI of T1N0 tumors were used: TCD_{50} = 30.89 Gy and $\gamma 50$ = 1.3%/% [18].

Patient selection and positioning

Nine patients with T1N0 left breast carcinoma treated with 3DCRT or conventional IMRT in our clinic were selected for this retrospective analysis of VMAT planning. The median age of the patients was 53 years (range: 38–63 years). The patients were simulated in the supine position with both arms raised above their head. They were scanned by computed tomography (CT) on a Philips Brilliance Big Bore simulator (Philips Medical Systems, Madison, WI) from the level of the larynx to the bottom of the lungs with a 5 mm slice thickness and slice spacing. The study was approved by the ethical committee of the General Hospital of Beijing Military Command. All patients provided written consent for storage of their medical information in the hospital database and for research use.

Delineation of target volumes and OARs

The delineation of target and OARs for all patients was performed by a single radiation oncologist with expertise in breast cancer treatment. The clinical target volume (CTV) consisted of the lumpectomy cavity with a margin of 15 mm modified to stay within the glandular tissue apparent on the CT scan. The planning target volume (PTV) was constructed by adding a 5 mm margin to the CTV and retracting the PTV to the tissue inside 3 mm of the skin to account for dose build-up during dose calculation. OARs delineated both lungs, the heart, the contralateral breast, anld the left anterior descending artery (LAD).

MLC specification and modeling

The Agility MLC has 80 pairs of leaves 5 mm wide at the isocenter, and the maximum field size is 40 cm × 40 cm. The maximum leaf speed is 3.5 cm s^{-1}, or up to 6.5 cm s-1 combined with a dynamic leaf guide (DLG). The BM MLC has 80 leaves with a leaf width of 4 mm at the isocenter, and the maximum field size is 21 cm × 16 cm. The leaf can move at a maximum speed of 3 cm s^{-1}. The minimum gap between opposite leaves is 5 mm. The maximum distance between leaves on the same leaf guide is 21 cm and the leaves have the ability to interdigitate. Two accelerators equipped with the two types of MLC were modeled in the Monaco treatment planning system (version 5.1, Elekta AB, Sweden).

VMAT planning and quality assurance

VMAT plans were generated on a Monaco TPS station using 6 MV photon beams from an Elekta Axesse linac with Agility MLC and a Synergy S linac with BM, respectively.

Two VMAT plans were designed for each patient. In each plan, the couch angle was set to 0° and the collimator angle was set to 90°. Two partial arcs of 220° ranging from 170° to 310° were selected. These angles were chosen to avoid direct irradiation to the spinal cord, contralateral breast, and contralateral lung. The prescribed dose to the PTV was 50 Gy in 25 fractions. The plans were normalized to cover 95% of the PTV with 100% of the prescribed

Table 1 Dose-volume constraints for PTV and OARs

Structures	Volume (%)	Dose (Gy)
PTV	95	50
Heart	≤10	30
Contralateral breast	≤15	3
Contralateral lung	≤15	3
Ipsilateral lung	≤70	5
	≤50	10
	≤30	20
	≤20	30

Table 2 Comparison of dose and volume parameters for OARs ($\overline{\chi} \pm s$)

OARs	Agility	BMC	t value	*p* value
Ipsilateral lung				
V5	64.80±8.11	82.02±6.05	-9.464	0.000
V10	40.86±6.63	50.71±5.99	-7.609	0.000
V20	25.82±5.00	28.47±4.49	-3.976	0.004
V30	17.18±3.88	18.63±3.92	-2.224	0.057
Contralateral breast				
V3	9.45±2.70	12.81±3.63	-3.160	0.013
Contralateral lung				
V3	7.21±1.98	7.78±1.31	-0.894	0.398
V5	2.03±1.11	1.94±1.22	0.145	0.888
Heart				
V5	66.00±6.79	73.04±7.80	-3.560	0.007
V10	37.57±8.32	41.41±10.75	-1.440	0.188
V20	12.16±3.12	12.13±3.76	0.036	0.972
V30	4.78±2.19	4.88±2.07	-0.278	0.788
LAD				
Dmean	22.10±7.11	23.91±7.69	-2.732	0.026

dose. The optimization objectives and constraints as listed in Table 1 were the same for all plans.

Plan delivery quality assurance (DQA) was performed with a Delta4 diode detector array (ScandiDos Inc., Sweden). The passing criterion with the gamma tests for DQA of the VMAT plan is 90% (3% dose difference, 3 mm distance to agreement) in our clinic.

Statistical analysis

Student's *t* test was used to compare means after an equal check of variance and statistical analyses were conducted using SPSS software (version 18.0, SPSS Inc., USA). The confidence interval was 95% and statistical significance was assigned to a *P*-value of < 0.05.

Results

Comparison of TCP

Statistical analysis showed a significant difference between the two plans based on the two types of MLC (*P* = 0.008). BM-based VMAT plans acquired a higher TCP than Agility-based VMAT plans.

Comparison of OARs dose-volume parameters

The dose-volume parameters of the OARs were listed in Table 2. Significant differences were observed in V5, V10, and V20 of the ipsilateral lung (*P* = 0.000, *P* = 0.000, *p* = 0.004), V3 of the contralateral breast (*P* = 0.013), V5 of the heart (*P* = 0.007), and the Dmean of LAD (*P* = 0.026). Agility-based VMAT plans spared more normal tissue when irradiating tumors.

Plan delivery efficiency

Delivery efficiency was assessed by measuring the MUs per fraction and the beam delivery time for each plan (Table 3). There was no significant difference between the two plans in terms of MU required. However, the delivery time for VMAT will not only depend on the number of MUs, but also on dose rate, speed of MLC movement, and gantry rotation. Therefore, the MU results of our current study do not reflect the actual delivery time. The actual delivery time with Agility was 35% less than that with BM.

Table 3 Number of MUs and delivery time with each type of MLC

Items	Agility	BM	*P* value
MUs	1140.1 ± 154.3	1133.2 ± 173.9	0.837
Delivery time (min)	2.6 ± 0.2	4.0 ± 0.2	0.000

Discussion

The MLC is very important in target shaping and OARs sparing. Many studies have investigated the effect of MLC leaf width on VMAT planning technique in several tumor sites [19–22]. In this study, we clearly showed that different MLC types have different radiobiological and, therefore, different clinical effects on breast cancer radiotherapy post conservative surgery. According to the calculation results from the EUD-based model, the BM VMAT plan may achieve a slightly higher TCP rate. Meanwhile, the Agility VMAT plan can achieve higher sparing of normal tissues.

However, it is well known that a longer treatment time will reduce cell death because prolonged treatments provide cells with an opportunity to repair DNA damage. Therefore, the faster leaf travel speed of the Agility MLC may be beneficial in decreasing DNA damage repair and improving treatment delivery efficiency.

The most important finding of this study is that VMAT can be delivered extremely efficiently with Agility and the delivery time was reduced for Agility by 35% compared with BM. The reasons may be as follows: (1)

Elekta BM was introduced into clinical work earlier, and it only supports the binned dose rate variation including five different dose rates: 600 MU/min, 300 MU/min, 150 MU/min, 75 MU/min, 37 MU/min; however, the Elekta Axesse linac utilized an upgraded integrity control system, which supported continuous variable dose rate variations with more available dose rate changes from 45 MU/min to 660 MU/min [23]. (2) The maximum leaf speed of Agility MLC is 6.5 cm s^{-1}, which is faster than that of BM MLC and is conducive to a reduction in time of delivery. This feature can improve the patients' comfort and reduce the intra-fraction motion of organs during radiation delivery.

Another issue demanding consideration is inter- and intra-fraction motion. The auto flash margin function embedded in the Monaco planning system can help solve the problem. Beyond that, the accuracy of the setup in VMAT can be further improved by using a breathing control device and an image guidance technique. The effect of breathing motion on plan delivery as well as calculation of EUD and TCP is currently under investigation by using four-dimensional computed tomography (4D-CT) in our department and the results will be reported in the near future.

Conclusions

For radiation therapy after conservative surgery for breast cancer, BM VMAT plans provide slightly higher TCP, but the delivery of Agility VMAT plans are significantly faster than those of BM VMAT plans. In addition, Agility VMAT plans can spare more normal tissues and achieve higher therapeutic ratios during irradiation of tumors.

Conflicts of interest

The authors declare that they have no competing interests.

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