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Original Research Article

A systematic review and meta-analysis of radiotherapy planning studies comparing multi leaf collimator designs

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ABSTRACT

Background and purpose: Several studies have investigated multi leaf collimator (MLC) leaf design. We performed a systematic review and meta-analysis of those studies to compare the impact of MLC leaf width used for different radiotherapy techniques.
Materials and methods: We decided to focus on 2.5, 3.0 and 5.0 mm leaf width MLCs as it appeared to be the most contentious area from literature. We adopted Cochrane and PRISMA guidelines and computed the association between MLC leaf width and conformity index (CI) across the selected studies as pooled mean difference (PMD) with 95% confidence interval.
Results: A total of 43 papers were selected from the literature search, of which ten compare MLC leaf width of 2.5 mm or 3.0 mm (MLC2.5 mm) versus 5.0 mm (MLC5 mm) in terms of CI. There was a slight, but significant, difference between MLC2.5 mm and MLC5 mm in favor of the former (mean difference −0.036; 95% confidence interval: −0.068 to −0.005). A subgroup analysis was performed by comparing techniques (intensity modulated radiation therapy vs conformal). In the intensity modulated radiation therapy (IMRT) subgroup, the difference between MLC2.5 mm and MLC5 mm appeared to be negligible (mean difference: −0.006; 95% confidence interval: −0.013 to 0.001) and not significantly different from zero. In the subgroup of studies which used conformal techniques, there was a significant difference between MLC2.5 mm and MLC5 mm (mean difference: −0.054; 95% confidence interval: −0.096 to −0.012).
Conclusions: Introduction of IMRT produced comparable target coverage (CI) between 2.5 or 5.0 mm leaf width MLCs.

1. Introduction

The multi leaf collimator (MLC) is one of the most critical components for the delivery of radiation oncology treatments using a linear accelerator [1]. Since the clinical introduction of MLCs in the early 1990s, several treatment planning system (TPS) and theoretical studies were conducted in order to attempt to determine the optimal MLC leaf design, in terms of target coverage and organ sparing [2–7]. These studies were based on TPS simulations and assessment of typical dose distribution parameters (such as conformity index, homogeneity index, dose volume histograms, tumor control probability, normal tissue complication probability, etc.).

There are many design characteristics in each MLC, such as leaf width, leaf tip design (single focus, double focus, not focused), tongue and groove presence, distance from the patient and leakage, to name a few. All of these characteristics may affect conformity to target and dose to surrounding structures. All papers found in a preliminary search focused on MLC leaf width as the main design parameter of interest, which suggests that authors of these papers consider this to be the biggest contributing factor to the ability to conform to the target and spare normal tissues [2–7]. Therefore, "MLC leaf width" was used as a search keyword and the remaining part of this analysis focused on this characteristic.

Jacob et al. [2] concluded that three collimator leaf thicknesses studied (10, 5 and 2.5 mm) were equally suitable for conformal coverage of the target volume and sparing of organs at risk (OARs) when using intensity modulated radiation therapy (IMRT). Wang et al. [3] concluded that a 4 mm MLC improved prostate planning target volume (PTV) dose coverage over a conventional 10 mm MLC in the treatment of prostate cancer using 6 MV for IMRT. With similar findings to Wang

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et al., but in contradiction to Jacob et al., Fujomoto et al. [4] demonstrated that the dose conformity of the PTV improved and the dose to bladder and rectum decreased for 3D conformal radiation therapy (3DCRT) and IMRT of prostate cancer using a 2.5 mm MLC compared to a 5 mm MLC.

Jin et al. [5] performed a study on cranial lesions and concluded that, for the DCA technique, there were significant dosimetric differences between different MLCs in terms of conformity indices. However, for the intensity modulated radiosurgery (IMRS)/IMRT technique, there was no significant difference of conformity index and target coverage between the 3 and 5 mm MLCs. Serna et al. [6] performed a study on brain lesions and showed a variation in conformity index of below 0.5% for volumetric modulated arc therapy (VMAT) and 3% for 3D-DCA, independent of the PTV volume. Therefore, for the VMAT technique, there was no significant improvement in conformation through the use of an MLC leaf width of 2.5 mm for small volumes. In contradiction with some of the above mentioned studies, Nill et al. [7] concluded that an improved PTV coverage and conformity was obtained for a 2.75 mm add-on MLC compared to the internal 4 mm MLC when using IMRT.

For the above mentioned studies, we noticed that there was no uniform agreement on the benefit of smaller leaf width. The difference seemed to be more evident for smaller lesions but, in some situations, it was reduced by the utilization of VMAT or IMRT techniques [6]. This lack of agreement, and the possibility that inverse planning techniques could have reduced the gap, triggered this study.

Since a good number of articles exist on the matter, we believed that a critical/systematic review had the potential to provide a good level of scientific evidence. The purpose of this analysis was to collect and group the existing literature concerning MLC leaf width and to determine if and what conclusions could be deduced. The focus was to determine if MLCs with different leaf width performed better in terms of target coverage and, if so, under what conditions. In general, smaller targets were considered the most challenging [2–7] and so we decided to focus on leaf widths of 5 mm or less.

2. Material and methods

In this review, the overall structure of the Cochrane analysis [8] or, in general, common rules identified as important in a systematic review according to PRISMA [9,10] guidelines, were adopted, as follows.

Search words were determined in advance. Searches were performed using PubMed (https://www.ncbi.nlm.nih.gov/pubmed), with search keywords “MLC leaf width”. Further papers were found using Google Scholar (https://scholar.google.com). In addition, all citations in the originally found papers were checked to identify the existence of any new papers. From the group formed by the above described search, all relevant publications relating to the subject matter (MLC comparison) were selected. Published peer-reviewed papers were chosen based on the simple criterion of being a comparison study between different MLC types in terms of conformity index. The data included in the selected publications were collected and the necessary statistical data (such as averages and standard deviations) were either used directly or calculated. If they could not be calculated, then the paper was not included in the review. Posters and presentations were not considered because they were not subjected to a peer review approach and, therefore, they have an uncertain level of evidence, in agreement with PRISMA guidelines. The last search was performed on 31st December 2015. No early cut-off date was determined. No subsequent papers relating to small leaf width comparison was found until end of February 2017. Two people, working independently, were involved in the selection process. Theoretical studies were included only if they produced data that could be used for the purposes of this study, such as standard deviations. Phantom studies were excluded because they were not thought to be representative of real clinical conditions.

It was decided to treat MLC leaf width of 2.5 mm or 3.0 mm as one subgroup, MLC2.5 mm, and MLC of leaf width 5.0 mm as the other subgroup, MLC5 mm. This was partly to increase the number of qualifying papers, but it was also judged that any difference between 2.5 mm and 3.0 mm would be much smaller than between the two subgroups MLC2.5 mm and MLC5 mm. In order to perform the analysis, it was necessary to reformulate the results from each of the papers into a common format. The statistical values chosen to estimate the pooled MLC effect were the mean difference (Diff) and its standard error [SE (Diff)]. To calculate them we used the method described in the Supplementary data.

The association between MLCs and conformity index reduction across the selected studies was then computed as pooled mean difference (PMD) with 95% confidence interval. The PMD was considered statistically significant if the 95% confidence interval did not include zero. PMD was estimated by pooling the study-specific estimates using random effect models [11], fitted using statistical analysis system (SAS) (proc Mixed) with a maximum likelihood estimate. These models provided estimates adjusted for the potential correlation within studies, as well as the heterogeneity between studies.

The homogeneity of the effect across studies was assessed by using the large sample test based on Cochrane’s Q statistics, which are distributed approximately as $\chi 2$ statistics. A p-value < 0.10 was used to indicate lack of homogeneity between effects. I2 statistics were also provided to quantify the percentage of total variation across studies that was attributable to heterogeneity rather than to chance [12]. The method of Macaskill et al. was used to assess publication bias [13]. This consists of a funnel-plot regression of the PMD on the sample size, weighted by the inverse of the variance.

A subgroup analysis was also performed to evaluate eventual differences between techniques. This was also triggered by the finding of Carosi et al. [14] and Serna et al. [6]. In particular, a comparison between MLC2.5 mm and MLC5 mm was performed in the subgroup of studies where IMRT or VMAT was used. Similarly, the same analysis was performed for the subgroup of studies that adopted 3DCRT or DCA. The hypothesis was that IMRT techniques reduce, or even annul, any differences between MLC2.5 mm and MLC5 mm, in terms of conformity index. In contrast, differences were expected in the subgroup of studies that adopted 3DCRT or DCA.

3. Results

From the literature search, 148 papers were found initially and 43 were selected according to the selection guidelines highlighted in the material and methods section (see Supplementary material for list of studies). Of these, ten papers compared MLCs with leaf widths of 2.5 mm or 3 mm versus 5 mm, in terms of conformity index, and were included in the final analysis (Table 1).

Three of the ten selected studies (Monk et al., Chern et al. and Fujimoto et al.) compared 3 mm leaf width versus 5.0 mm, while the others compared 2.5 mm leaf width versus 5.0 mm.

In total, 357 cases from those ten papers were included in the main analysis.

The conformity index of MLC2.5 mm for the whole group was slightly, but significantly, better compared to MLC5 mm. The pooled mean difference was -0.036 with a 95% confidence interval ranging between -0.068 and -0.005 ($p = 0.026$).

In the IMRT/VMAT subgroup, the difference between MLC2.5 mm and MLC5 mm appeared to be negligible (mean difference: -0.006; 95% confidence interval: -0.013 to 0.001) and not significantly different from zero ($p = 0.064$). In contrast, in the subgroup of studies that used conformal 3DCRT/DCA techniques, MLC2.5 mm results were significantly different to MLC5 mm (mean difference: -0.054; 95% confidence interval: -0.096 to -0.012; $p = 0.02$). This is shown graphically by a forest plot in Fig. 1.

Within the IMRT/VMAT subgroup, there was a substantial homogeneity between studies. In the 3DCRT/DCA subgroup, in contrast, the heterogeneity remained quite large. However, all studies but one (Serna

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