INFORMATION BRIEF (RAPID REVIEW)

TOMOTHERAPY FOR CANCER TREATMENT

Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia
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TITLE: TOMOTHERAPY FOR CANCER TREATMENT

PURPOSE

To review the effectiveness, safety and cost-effectiveness of Tomotherapy for cancer treatment based on request from the Director of Medical Practice Division, Ministry of Health Malaysia who received an enquiry regarding the procedure from a private hospital.

BACKGROUND

According to the Malaysia National Cancer Registry Report 2012-2016, a total of 115,238 new cancer cases were registered for the period. The incidence rates for all sites combined were increased by 2.3 in females and slightly reduced by 0.8 in males per 100,000 populations when the last five-year period (2012–2016) was compared with the period of 2007–2011.[1]

Imaging has always been a necessary prerequisite for radiation therapy. Presently, an interaction between these two fields of technology is observed. The discovery of X-rays more than a century ago provided the possibility to locate internal organs in the human body and plan radiation delivery with rectangular fields using two-dimensional (2D) transmission images up to the mid-1970s. Later, the introduction of computed tomography (CT) in clinical practice resulted in high quality three-dimensional (3D) images, which allowed precise definition of tumour shape and location.[2]

Technological advances in radiation oncology such as three-dimensional conformal radiation therapy (3DCRT) and intensity-modulated radiation therapy (IMRT) allow the shaping of the dose distributions in patients, with a very high degree of conformity and precision. The application of high-dose gradients provides opportunities for escalating tumour doses resulting in a better chance of the elimination of cancerous cells while still sparing healthy, sensitive organs. At the same time, such highly localised dose distributions may result in a partial target miss and/or risk of organ damage if on the day of treatment the patient setup and/or anatomy are different from that of the imaging study used during planning. If changes in the patient's anatomy are not detected, the treatment could be compromised.[2]

Tomotherapy technique was developed in the early 1990s. It uses small megavoltage x-ray source mounted in a similar fashion to a CT x-ray source, and the geometry

provided the opportunity to provide CT images of the body in the treatment setup position. It uses an integrated computed tomography scanner to improve the accuracy of radiotherapy treatment. During treatment, the patient lies on a couch that moves continuously through a rotating ring. Radiation is delivered from all angles as the ring turns and the couch moves through the gantry. Tomotherapy allows continuous delivery of radiation beams from all angles by using a slice by slice process or one layer at a time which enables all areas of a tumour to receive radiation. The radiation is delivered helicoidally, allowing highly conformal shaping of dose distribution while minimising radiation exposure to healthy tissues.[3]

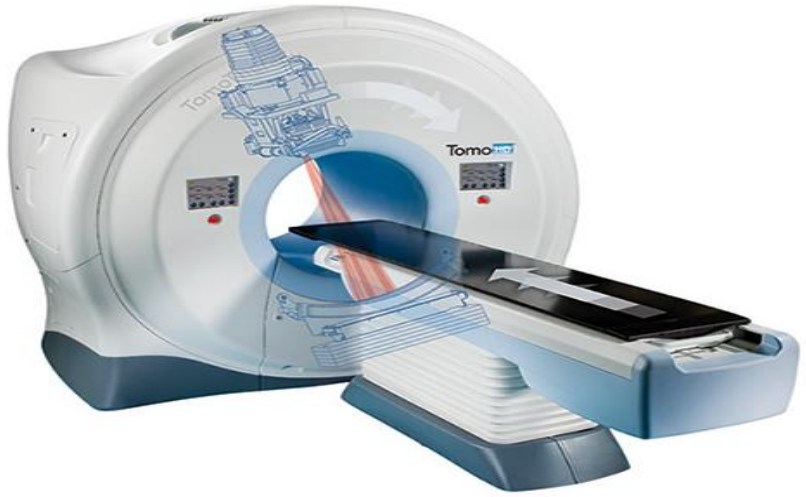

Figure 1: Image of Tomotherapy device[4]

EVIDENCE SUMMARY

There were 1301 articles retrieved on the Tomotherapy for cancer from the scientific databases such as Medline, EBM reviews, Pubmed and from the general search engines [Google Scholar and US Food and Drug Administration (USFDA)] using the search term *neoplasms, cancer, tumour, tomotherapy, helical tomotherapy*. Last search was conducted on 23th August 2022. Most of the articles retrieved were on dosimetric studies of tomotherapy. There were also studies retrieved on intensity-modulated radiotherapy which were not specific to tomotherapy. A total of nine studies were included in this review, consisted of two systematic reviews, four randomised clinical trials, one feasibility study, one retrospective analysis and one cost-effectiveness analysis.

EFFICACY/ EFFECTIVENESS

Lung cancer

Bavandpour E et al. conducted a systematic review to evaluate the effectiveness and safety of stereotactic radiosurgery (SRS) techniques such as cyberknife, gammaknife and tomotherapy in the treatment of lung cancer. They systematically searched the databases for articles evaluating the efficacy and safety of radiation technologies applicable in stereotactic body radiation therapy. Selection of articles, data extraction and quality assessment were conducted by two reviewers. Outcome of interest were local tumour control, survival rate and toxicity. A total of 12 retrospective studies with 616 patients examining the efficacy and safety of a certain technology were included in the review. However, no study was found on the comparison of tomotherapy and cyberknife. There was also no study retrieved on the application of gamma knife for lung tumour treatment. They reported that, six retrospective studies were retrieved on the tomotherapy. Four studies were on non-small cell lung cancer (NSCLC), one study on NSCLC/ squamous cell carcinoma and adenocarcinoma, and population of another one study was not mentioned. Local tumour control in different lung tumours varied from 63% to 100%. The two years and five years survival rate was 73% and 56% respectively.[5]

Meanwhile for the cyberknife, there were six studies retrieved. Two studies were on NSCLC, one study on NSCLC/ solitary lung metastases, one study on NSCLC/ metastatic lung tumours, one study on lung metastases and one study did not mention the population. The local tumour control ranged from 65% to 100%. The one year survival rate was 80% to 83%, two years survival rate was 60% to 62% and five years survival rate was 16%.[5]

Hepatocellular carcinoma

Huang CM et al. conducted a feasibility study to evaluate the efficacy and toxicity of helical tomotherapy for cirrhotic patients with unresectable hepatocellular carcinoma (HCC). A total of 38 HCC patients treated with helical tomotherapy were enrolled from March 2008 to September 2010. Treatment planning was generated using Tomotherapy planning software, version 4.0 (Tomotherapy, Madison, WI). Helical tomotherapy was delivered once per day, five times a week. Before each treatment, a megavoltage CT scan was performed to correct the displacement of tumours and internal organs automatically or manually. Median radiation dose was 54 Gy (range:46 to 71.8) delivered in 1.8 to 2.4-Gy fractions. The planning target volumes were 241.2 ± 153.1 cm^3 (range: 45.8 to 722.4). Treatment responses were assessed in three to six months after helical tomotherapy. They reported that, there was a complete response in two patients (5.2%), partial response in 18 patients (47.4%), stable disease in 13 patients

(34.2%), and progressive disease in five patients (13.2%). The median overall survival was 12.6 months, and one- and two-year overall survival rates were 56.2% and 31.7%, respectively. Responders had better overall survival than non-responders (23.6 versus 5.8 months, p< 0.001). The one- and two-year overall survival rates for responders were 68.3% and 57%, respectively, while for non-responders, they were 0%. The one- and two-year local control rates were 88.2% and 82.3%, respectively.[6]

Breast cancer

Parjis V et al. conducted a study to assess the long term impact of the trial on respiratory-related patient-reported outcomes (PRO) via single center, phase III, randomised controlled trial comparing tomotherapy (TT) system versus post-surgery conventional radiotherapy (CR) for breast cancer (TomoBreast). The trial was conducted in 2007 to 2011. A total of 123 women were randomised to either control group (n=64) or experimental (n= 59). Conventional radiotherapy was delivered 50 Gy in 25 fractions/5 weeks to breast/chest wall and regional nodes if node-positive, with a sequential boost (16 Gy/8 fractions/1.6 weeks) after lumpectomy. Meanwhile, tomotherapy was delivered 42 Gy/15 fractions/3 weeks to breast/chest wall and regional nodes if node-positive, 51 Gy simultaneous-integrated-boost in patients with lumpectomy. Patient-reported outcomes were assessed using the European Organization for Research and Treatment of Cancer questionnaire QLQ-C30. The scores were converted into a symptom-free scale, 100 indicating a fully symptom-free score, 0 indicating total loss of freedom from symptom. Changes of PRO over time were analysed using the linear mixed-effect model. Survival analysis computed time to > 10% PRO-deterioration. A post-hoc cardiorespiratory outcome was defined as deterioration in either dyspnoea, fatigue, physical functioning, or pain.[7]

They reported that the PRO at baseline were below the nominal 100% symptom-free score, notably the mean fatigue-free score was 64.8% versus 69.6%, pain-free was 75.4% versus 75.3%, and dyspnoea-free was 84.8% versus 88.5%, in the TT versus CR arm, respectively although the differences were not significant. Mixed-effect modelling on early ≤2 years assessment showed that all three scores deteriorated, significantly for fatigue, p ≤0.01, without effect of randomisation arm. However, modelling on late assessment beyond two years, showed that TT versus CR was not significantly associated with changes of fatigue-free or pain-free scores but was associated with a significant 8.9% improvement of freedom from dyspnoea (p = 0.035). From the survival analysis of the time to PRO deterioration, TT showed an improved 10-year survival free of cardiorespiratory deterioration from 66.9% with CR to 84.5% with TT (p=0.029).[7]

Another study from the same cohort was conducted by Verbanck S et al to assess the long term effect of two radiation regimens of 3D conformal radiation (CR) and hypofractionated tomotherapy (TT). A total of 84 patients with breast cancer was assessed at baseline, after 3 months and after one, two, three and ten years. Outcome measurements were forced vital capacity, total lung capacity (TLC) and diffusing capacity (TLco). They reported that radiation therapy−induced lung function changes over ten years were similar for both treatment arms. In the subgroup, as well as in the entire patient cohort, the incurred pulmonary restriction in terms of TLC and TLco showed a greater decline at three months for CR versus TT. However, at ten years, there was no significant difference detected between CR and TT (p=0.9 for TLC and p=0.2 for TLco in the entire patient cohort). Of the patients with normal TLC and TLco at baseline (ie, above lower limits of normal), respectively 94% and 96% were still normal 10 years later.[8]

Versmessen H et al. compared health related quality of life (HRQOL) in stage I and II breast cancer patients who received either conventional radiotherapy (CR) or hypofractionated tomotherapy (TT). The patients were the same cohort from TomoBreast clinical trial. A total of 121 patients were included in the analyses. Patients completed the European Organisation for Research and Treatment of Cancer (EORTC) general cancer quality of life score (QLQ-C30) questionnaire and its breast cancer module (QLQ-BR23) questionnaires. The mean score was calculated at baseline, the end of radiotherapy, and at three months and one, two, and three years post-radiotherapy. They reported that on the last day of radiotherapy, the global health score was significantly worse in TT patients than CR patients (p = 0.0287) and the social functioning score was worse in TT patients than CR patients, but the difference was not significant (p = 0.0635). However, analysis using repeated measurements of ANOVA with the Bonferroni correction did not show any significant differences in these scores between treatment arms. At three months post-radiotherapy, there were clinically increases in the role- and social-functioning scores in TT patients. During the period from three months to two years post-radiotherapy, there were faster improvements in the physical-, cognitive-, and emotional-functioning scores in TT patients than CR patients, but those differences were not significant.[9]

<u>Oral Cavity Cancer</u>

Hsieh CH et al. conducted a retrospective data analysis to analyse postoperative locoregional failure patterns, clinical outcome and toxicity among postoperative oral cavity cancer patients treated with helical tomotherapy. A total of 53 patients were enrolled between December 2006 and November 2015. Radiation therapy, delineation of target volumes, chemotherapy and follow up data was recorded. They descriptively reported that the three- and four-year overall survival (OS), disease free survival (DFS),

locoregional control (LRC), and metastatic free survival (MFS) rates were 71.5%, 59.0%, 72.1%, and 83.9% respectively at three years and 59.7%, 59.0%, 66.1% and 83.9% respectively at four years. The 4-year LRC rates of infield failure and out-of-field failure were 70.7% and 95.6%, respectively. The four-year local and regional control survival rates were 76.4% and 94.3%, respectively.[10]

Mixed cancer types

Yang ZX et al. conducted a systematic review to rapidly assess the effectiveness, safety, costs, and applicability of helical tomotherapy to provide available best evidence for decision-makers of health policies. They systematically searched for the databases including PubMed, EMbase, The Cochrane Library and other professional websites. Two reviewers independently screened literature according to the inclusion and exclusion criteria, extracted data, assessed quality, and performed descriptive analysis. They included 150 studies, encompassing five health technology assessments (HTA), 18 clinical controlled trials, and 127 observational studies. They reported that the included HTAs were published during 2006–2009, providing fairly less evidence of low quality and the results of 145 primary studies showed that: helical tomotherapy had been used mainly in the treatments of 14 kinds of cancer, with low total toxicity and high survival rates. Although the quality of the included studies was poor, there was much evidence about prostate cancer, head and neck cancer, nasopharynx cancer, cervical cancer, lung cancer and liver cancer, with enough sample and fairly reliable results in HT efficacy and safety.[11]

Previously, MaHTAS has conducted a systematic review on Tomotherapy in 2006. The report concluded that there was limited clinical evidence available to-date describing the use of tomotherapy. However, it was recommended to monitor the technology until more research/data establishes its effectiveness, safety and cost effectiveness.[12]

SAFETY

A randomised clinical trial was conducted by Parjis HV et al. to report early toxicities comparing conventional radiotherapy with hypofractionated tomotherapy for post-operative treatment of breast cancer up to three years. The trial involved 70 women with stage T1-3N0M0 or T1-2N1M0 breast cancer completely resected by tumorectomy (BCS) or by mastectomy (MA). They were randomised to receive either CR 25x2 Gy/5 weeks by tangential fields on breast/chest wall, plus supraclavicular-axillary field if node-positive, and sequential boost 8x2 Gy/2 weeks if BCS (cumulative dose 66 Gy/7 weeks) in control group versus 15x2.8 Gy/3 weeks, including nodal areas if node-positive and simultaneous integrated boost of 0.6 Gy if BCS (cumulative dose 51 Gy/3

weeks) in the experimental group. Outcome of interest were pulmonary and heart function. One patient dropout leaving 69 participants where 32 were assigned to control group (21 BCS, 11 MA) and 37 were assigned to experimental group (20 BCS, 17 MA). They reported that, skin toxicity of grade ≥ 1 at two years was 60% in conventional radiotherapy versus 30% in hypofractionated tomotherapy arm. Heart function showed no significant difference for left ventricular ejection fraction at two years (conventional radiotherapy 4.8% versus hypofractionated tomotherapy 4.6%). Pulmonary function tests at two years showed grade ≥1 decline of forced expiratory in one second (FEV1) in 21% of conventional radiotherapy versus 15% of hypofractionated tomotherapy and decline of diffusing capacity of the lung carbon monoxide (DLco) in 29% of conventional radiotherapy versus 7% of hypofractionated tomotherapy ($p = 0.05$).[13]

Bavandpour E et al. in their systematic review reported that the mortality rate of patients up to the completion of the treatment course varied from 0% to 34%.[5]

Huang CM et al. in their feasibility study reported that there were five patients (13.2%) had grade 3 or greater liver toxicity, and one patient (2.6%) had a grade 3 gastric ulcer. However, there was no treatment-related liver failure or death was documented in the study.[6]

Hsieh CH et al. in their retrospective data analysis reported that the rates of grade 3 dermatitis, mucositis, and dysphagia were 11%, 34%, and 13%, respectively. There was no grade 3 xerostomia was noted. Grade 2 xerostomia was 33% at month 6 and declined to 0 at month 48.[10]

Several brands of Tomotherapy device such as Hi-Art System, TomoHD, Accuracy and Radixact® System had received 510 (k) from USFDA and classified as class II medical device.[14] Tomotherapy device Hi-Art System was registered with Malaysian Medical Device Authority.[15]

COST-EFFECTIVENESS

There was no evidence retrieved on the cost-effectiveness specific to tomotherapy. However, there was one study conducted by Xie Y, Guo B and Zhang R to perform cost-effectiveness analyses of standard of care (SOC) and advanced post-mastectomy radiotherapy (PMRT) techniques including intensity-modulated radiotherapy (IMRT), standard volumetric modulated arc therapy (STD-VMAT), non-coplanar VMAT (NC-VMAT), multiple arc VMAT (MA-VMAT), Tomotherapy (TOMO), mixed beam therapy (MIXED), and intensity-modulated proton therapy (IMPT). They estimated the cost-effectiveness of various techniques over 15 years using markov model. A cohort of

women (55-year-old) was simulated in the model, and radiogenic side effects were considered. Transition probabilities, utilities, and costs for each health state were obtained from literature and Medicare data. Model outcomes include quality-adjusted life-years (QALYs) and incremental cost-effectiveness ratio (ICER). They reported that. STD-VMAT has an ICER of USD 32,617/QALY relative to SOC; TOMO is dominated by STD-VMAT; IMRT has an ICER of USD 19,081/QALY relative to STD-VMAT; NC-VMAT, MA-VMAT, MIXED are dominated by IMRT; IMPT has an ICER of USD 151,741/QALY relative to IMRT. One-way analysis shows that the probability of cardiac toxicity has the most significant impact on the model outcomes. The probability sensitivity analyses showed that all advanced PMRT techniques are more cost-effective than SOC at a willingness-to-pay (WTP) threshold of USD 100,000/QALY, while almost none of the advanced techniques were more cost-effective than SOC at a WTP threshold of USD 50,000/QALY.[16]

CONCLUSION

There was limited evidence retrieved to suggest that Tomotherapy is effective and safe for cancer treatment. The limited evidence showed, the effect was similar with conventional radiotherapy in long duration.

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