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Safety and Efficacy of Tomotherapy for Lung Cancer Compared to Other Radiotherapy Techniques: A Systematic Review

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Abstract

Context: Lung cancer is one of the most common cancers worldwide with high mortality and short survival rate. Radiotherapy is one of the treatment modalities in patients who are non-surgery candidates or refuse surgery.
Objectives: The current study aimed at evaluating the effectiveness and safety of this technique compared to similar ones for lung cancer treatment.
Methods: In order to answer the research question and find the available evidence, after the development of the search strategy, Pubmed, Cochran, Ovid, Medline, and DARE databases were searched and related articles were selected based on the inclusion criteria. Then, we chose all studies that had the PICO acceptance criteria (Participants: adults with lung cancer; Intervention: tomotherapy; Comparisons: tomotherapy with Cyberknife; Outcomes: local tumor control (LTC), survival rate (SR), complications, and degree of toxicity). The quality assessment of the studies was conducted using the CASP (Critical Appraisal Skills Programme) checklist. Two independent search engines evaluated the articles in terms of methodology, and information was extracted from the papers.
Results: Overall, 12 retrospective studies with 616 patients were found examining the efficacy and safety of a certain technology. According to the results of the studies, the local tumor control (LTC) index varied from 63% to 100%. The two and five-year SRs were 73% and 56%, respectively. In addition, the mortality rate of patients until the completion of the treatment course was 34%, indicating the higher efficacy of tomotherapy than the efficacy of other similar techniques. The toxicity of tomotherapy was less than that of Cyberknife, which indicates its more safety.
Conclusions: According to the epidemiology of cancer, especially lung cancer, and due to aging of the population in Iran, and considering the higher efficacy and safety of tomotherapy in comparison with other similar technologies, i.e., Cyberknife and Gamma Knife, tomotherapy is a superior technique in the control and treatment of lung cancer although other aspects, such as cost-efficacy, should be considered.

Keywords: Tomotherapy, Lung Cancer, Cyberknife, Gamma Knife

1. Context

Lung cancer is one of the most common cancers worldwide with a high rate of mortality and short survival rate (1). There are two main types of lung cancer, small-cell lung carcinoma (SCLC) and non-small-cell lung carcinoma (NSCLC). The latter type of malignancy (NSCLC) accounts for about 90% of all lung cancer cases with a low progression rate compared to SCLC (1). However, SCLC grows more aggressively and rapidly than NSCLC; hence, the treatment choice for lung cancer varies depending on its type; nevertheless, SCLC accounts for less than 20% of all lung cancer cases (1).

Lung resection surgery is performed in 20% - 25% of patients. However, about 20% - 30% of patients with lung cancer are not eligible for surgery or refuse to undergo surgery (1). In recent years, the strategy for the treatment of lung malignancies has remarkably changed while until 20 years ago, the surgery had been the first-line treatment for NSCLC. New technologies in radiation therapy have provided more concentrated, focused therapy, with improved efficacy and decreased toxicity compared to traditional external beam radiation (2). Stereotactic radiation therapy

(SRS) has been used for many years for the treatment of intracranial lesions not amenable to surgical resection. The stereotypic radiosurgery (SRS), which is a wide spectrum of tightly focused beams, is applied to tumors and lesions in the brain, neck, lung, liver, and spine, but is called SBRT when applied to other organs (2).

Stereotactic body radiation therapy (SBRT) was first used by Biomangren et al. in 1995. It is not a traditional type of surgery, as there is no incision. Instead, SRS or SBRT is a technique that uses 3D imaging with high doses of radiation to target the affected area with minimal impact on surrounding tissues (3). Technologies that can be run based on SRS are Cyberknife, Gamma Knife, and tomotherapy.

2. Objectives

The current study aimed at comparing the safety and efficacy of SRS techniques in the treatment of lung cancer.

3. Methods

To achieve the goals hinted in the research question, one of the most important steps was the comprehensive search of evidence in Iran and other countries for use in answering the question. To comprehensively search databases, finding appropriate keywords that comprise the study PICO seems essential. Here, after selecting keywords, the available databases, particularly PubMed, Cochran, Ovid, Medline, and DARE, were searched. In addition, to increase the coverage and search sensitivity and to get the maximum number of articles, Google and Google Scholar search engines were also run using the keywords. To retrieve the related articles in Persian databases, the SID and other Persian databases such as Irandoc, Iranmedex, and magiran were searched (Table 1).

Table 1. Search Strategy

No.	Pubmed and Cochran Search Strategy	Ovid Medline Search Strategy
#1	"Tomo Therapy"	"TomoTherapy".mp
#2	MeSH descriptor "TomoTherapy" exploded all trees	"cyber knife".mp
#3	(#1 or #2)	"gamma knife".mp
#4	"cyber knife"	"lung cancer".mp
#5	MeSH descriptor "cyber knife" exploded all trees	(#1 or #4)
#6	(#4 or #5)	(#2 or #4)
#7	(#3 and #6)	(#3 or #4)
#8	"lung cancer"	(#5 and #6)
#9	MeSH descriptor "lung cancer" exploded all trees	(#7 and #8)
#10	(#8 and #9)	(#8 and #9)
#11	Gamma knife	"S.R".mp
#12	MeSH descriptor "Gamma knife" exploded all trees	rev # .mp
#13	#11 or #12	(#10 and #11)
#14	#10 and #13	(#10 and #12)
#15	#7 and #14	

3.1. Selection and Quality Assessment Criteria

To evaluate the retrieved studies, the CASP (Critical Appraisal Skills Programme) checklist, a standard tool for critical appraisal, was used. Some of the retrieved articles were excluded based on the title; the rest was appraised based on the inclusion criteria (PICO), and then the full texts of the eligible articles were read to enroll the most relevant ones in the study.

3.2. Inclusion and Exclusion Criteria

All clinical trials, retrospective, and review articles were included. After selecting the studies, the eligible clinical trials and retrospective articles evaluating the efficacy and safety of radiation technologies applicable in SBRT were assessed in terms of applied technology and then were compared. The methodology and quality of the studies were evaluated independently by two experts for each article. However, no study was found on the comparison of tomotherapy and Cyberknife. Thus, we chose all the studies that had the eligibility criteria examining the effectiveness and safety of a given technology.

Participants: Adults (over 18-years-old) with lung cancer

Intervention: Tomotherapy

Comparisons: Tomotherapy with Cyberknife

Outcomes: Local tumor control (LTC), survival rate (SR), complications, and degree of toxicity

4. Results

4.1. Efficacy and Safety of Tomotherapy for Lung Tumors

To the best of the authors' knowledge, there were a few studies on the efficacy of helical tomotherapy in the treatment of lung cancer and the worse thing was that these finite articles had not very high quality. In general, no randomized clinical trial was found in this regard although six retrospective studies were found particularly on the efficacy of tomotherapy in the SR of patients with lung tumors using LTC indices (3-8). In the study by Monaco et al. (3) in Italy using the radiation dose of 67.5 Gy/30 fractions at 2.5

Gy per fraction, the results showed that this method with a maximum dose per fraction was effective in the treatment of lung cancer without increasing the outcomes.

The study by Bral et al. (4) reported that the dose of 67.2 Gy plus chemotherapy was the safest radiation dose with acceptable toxicity. In phase 2 of the same study, aiming to increase the local response rate of 2.24 Gy per fraction, they increased the radiation dose to 2.36 Gy per fraction and indicated that based on the maximum tolerated dose (MTD), outcomes, and the degree of toxicity, increasing the dose until 2.24 Gy per fraction was unsafe. In a retrospective study, Song et al. (5) (based on tumor grade) increased the receiving dose from 60 to 66 Gy/14 - 18 fractions at 2.4 Gy per day (6).

The results of the reviewed studies showed that the LTC success in different lung tumors varied from 63% (5) to 100% (3); the highest and lowest LTC success rates belonged to primary lung tumors; it was also 100% in terms of NSCLC (Table 2).

In addition, the two-year SR was 73% and the five-year SR was 56%. The mortality rate of patients up to the completion of the treatment course varied from 0% (3) to 34% (5).

4.2. Efficacy and Safety of Cyberknife for Lung Tumor Treatment

According to the findings of the current study on the efficacy and safety of Cyberknife in the treatment of lung tumors, totally six articles were retrieved of which, five recommended the LTC as an effective indicator for Cyberknife efficacy in the treatment of lung tumors, which varied from 65% to 100% (9-14).

The highest efficacy of Cyberknife belonged to the treatment of NSCLC and the lowest was observed for the treatment of SCLC (Table 3). The one-year SR was 80% - 83%, the two-year SR was 60% - 62%, and the five-year SR was 16%.

There was no report of mortality rate due to Cyberknife in the examined studies, except for the study by Abreu et al. that reported the mortality rate of 2.7% due to SBRT (1).

4.3. Efficacy and Safety of Gamma Knife for Lung Tumor Treatment

No study was found on the application of Gamma Knife for lung tumor treatment. Since this advanced technique has high precision in the treatment of small targets, it is only applied to the treatment of small intracranial lesions and targets within the head of < 3 - 4 cm in diameter on average (15).

4.4. Comparison of the Efficacy of Tomotherapy, Cyberknife, and Gamma Knife for Lung Tumor Treatment

In the treatment of lung tumors, due to their specific conditions such as the movement of the target due to breathing and placement in the vicinity of a vital tissue (heart), tomotherapy, Cyberknife, and Gamma Knife are the suitable radiotherapy techniques for radiosurgery (16).

In the systematic review of 12 articles (Figure 1.), more than 616 patients were included. The evidence suggested that Gamma Knife was not applicable to the treatment of lung tumors due to its high precision in the treatment of small targets and intracranial lesions (17).

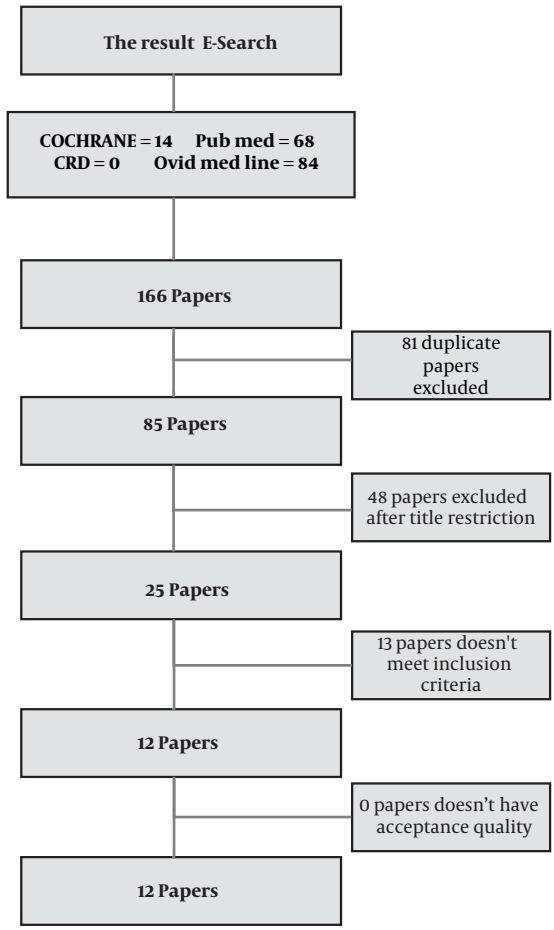

Figure 1. The flow of the papers through the study

Based on the evidence found in the current study, tomotherapy has higher efficacy than Cyberknife in terms of efficacy indices, i.e., LTC and SR. Tomotherapy received FDA clearance for safety indicators in 2008 (18). However, radiotherapy, despite its many benefits, is associated with various outcomes, some of which were investigated in the reviewed studies.

In the treatment of patients with lung cancer, tomotherapy minimizes the risk of respiratory problems and esophageal damage (17). In order to repeat radio-

Table 2. The Details of Studies for Efficacy and Safety of Tomotherapy

Item	Authors/Year (Ref.)	Type of Study	Number of Samples	Follow-Up Time, mo	Type of Tumor	Studied Outcomes
1	Monaco et al./2012 (3)	CCT	35	12.3 (6 - 22)	NSCLC	Toxicity, overall treatment efficacy
2	Casutt et al./2014 (7)	CCT	16	-	NSCLC	Lc, SR
3	Bral et al./2010 (4)	CCT	34	17	NSCLC	Lc, SR, OS, degree of toxicity
4	Song et al./2010 (5)	CCT	37	18	NSCLC	Lc, SR, OS, degree of toxicity
5	Nagai et al./ 2014 (6)	CCT	72	20	-	Lc, OS
6	Chen et al./2018 (8)	CCT	21	48 (36.9 - 59.1)	NSCLC, squamous cell carcinoma, and adenocarcinoma	CR, PR, SD, PD, ORR, OS

Abbreviations: CR, complete response; LC, local control; OS, overall survival; ORR, overall response rate; PD, progress disease; PR, partial response; SD, stable disease.

Table 3. The Details of Studies for the Efficacy and Safety of Cyberknife

Item	Authors/Year (Ref.)	Type of Study	Number of Samples	Follow-Up Time, mo	Type of Tumor	Studied Outcomes
1	Gibbs and Loo/2010 (12)	CCT	34	17	NSCLC	Ls, OS, SR, degree of toxicity
2	Whyte et al./2003 (9)	CCT	23	7 (1 - 26)	-	Overall treatment efficacy
3	Le et al./2006 (10)	CCT	32	-	NSCLC/solitary lung metastases.	Lc, degree of toxicity
4	Jen et al./2014 (11)	CCT	55	34	NSCLC/metastatic lung tumors.	Lc, SR, BED, degree of toxicity
5	Nuyttens et al./2006 (13)	CCT	22	4 (2 - 11)	NSCLC	Lc, SR
6	Brown et al./2008 (14)	CCT	35	18	Lung metastasis	Lc

therapy in patients already undergone radiotherapy, tomotherapy did not cause complications and reduced the risk of ulceration and pain caused by repeated radiotherapy (new treatment paradigm) (17). The toxicity degree was acceptable in both techniques (tomotherapy and Cyberknife), which confirms their safety (18).

Based on the HTA study results in China, helical tomotherapy is a more effective and safer technology for the treatment of different cancers, but further qualitative studies with long-term follow-ups are required to confirm the available findings and investigate the long-term outcomes of helical tomotherapy (19).

The results of a reviewed clinical trial showed that in general, the use of tomotherapy is safe at the clinical level and its acute and chronic toxicities are considered acceptable and applicable to all parts of the body (19).

Tomotherapy is used to treat complicated, large tumors at vital body points (17). The degree of toxicity in tomotherapy is less than that in Cyberknife and therefore, it is a safer technique (19). The risk of sedimentation in the overlapping areas is minimized in tomotherapy due to the capability of 360-degree rotation and radiation at all angles (20). The duration of each treatment session is short with tomotherapy compared to Cyberknife. Shorter irradiation duration (40 minutes vs. 27 minutes) shortens the queue time (21). Therefore, tomotherapy is suitable for crowded centers.

Tomotherapy is an appropriate method for patients with obesity, claustrophobia, or those with complications such as pain, bone lesions, or neurological problems (20). Some features such as no need for surgery, especially in patients who are ineligible for surgery, and the short course of treatment are among other advantages, which are roughly the same in both methods.

5. Discussion and Conclusions

Based on the current study findings, the efficacy of the three methods, tomotherapy, Cyberknife, and Gamma Knife, as radiosurgery or radiotherapy techniques, was observed in patients with lung cancer. Gamma Knife is not applicable to the treatment of pulmonary lesions. Cyberknife and tomotherapy are almost identically effective in the treatment of lung lesions based on LTC indices. Little difference between the technologies may be attributed to the type of tumor, the uncertainty of patient conditions in different studies, and differences in target groups. As no meta-analysis was conducted in this regard, such differences cannot be emphasized. However, the five-year SR was higher for tomotherapy (54% vs. 16%).

Nevertheless, the complications and consequences of tomotherapy are less; therefore, tomotherapy is superior to Cyberknife.

Due to the increasing incidence of cancer in Iran (i.e., lung, prostate, and gastrointestinal tract cancers), tomotherapy is a more appropriate technique. Moreover, considering the increase in the number of old people, the number of lung cancer cases will increase in the near future, which necessitates the use of tomotherapy.

Based on the findings, tomotherapy is considered an effective and safe technique for the treatment of lung cancer, but there are challenges in the selection of tomotherapy as the treatment of choice for lung cancer. To the best of the authors' knowledge, no economic evaluation has been performed in this regard. According to available evidence, the cost of purchasing, installing, and launching tomotherapy devices is very high (5.3 to 5.5 million Canadian dollars) (22). There was no evidence of long-term complications due to tomotherapy. Its application requires trained and expert manpower.

5.1. Sanctions and Challenges Ahead

Totally, ignoring the abovementioned barriers and considering the epidemiology of cancer in Iran, and the higher efficacy and safety of tomotherapy, it is currently a superior technique for the control and treatment of lung cancer; however, it is suggested that its cost-efficacy be considered in practice before its application.

Footnotes

Conflict of Interests: The authors declare no conflicts of interest.

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References

1. Abreu CE, Ferreira PP, de Moraes FY, Neves WF Jr, Gadia R, Carvalho Hde A. Stereotactic body radiotherapy in lung cancer: An update. *J Bras Pneumol*. 2015;**41**(4):376–87. doi: 10.1590/S1806-37132015000000034. [PubMed: 26398758]. [PubMed Central: PMC4635958].
2. Baker S, Dahele M, Lagerwaard FJ, Senan S. A critical review of recent developments in radiotherapy for non-small cell lung cancer. *Radiat Oncol*. 2016;**11**(1):115. doi: 10.1186/s13014-016-0693-8. [PubMed: 27600665]. [PubMed Central: PMC5012092].
3. Monaco A, Caruso C, Giammarino D, Cianciulli M, Pressello MC, Donato V. Radiotherapy for inoperable non-small cell lung cancer using helical tomotherapy. *Tumori*. 2012;**98**(1):86–9. doi: 10.1700/1053.11504. [PubMed: 22495706].
4. Bral S, Duchateau M, Versmessen H, Verdries D, Engels B, De Ridder M, et al. Toxicity report of a phase 1/2 dose-escalation study in patients with inoperable, locally advanced nonsmall cell lung cancer with helical tomotherapy and concurrent chemotherapy. *Cancer*. 2010;**116**(1):241–50. doi: 10.1002/cncr.24732. [PubMed: 19918925].
5. Song CH, Pyo H, Moon SH, Kim TH, Kim DW, Cho KH. Treatment-related pneumonitis and acute esophagitis in non-small-cell lung cancer patients treated with chemotherapy and helical tomotherapy. *Int J Radiat Oncol Biol Phys*. 2010;**78**(3):651–8. doi: 10.1016/j.ijrobp.2009.08.068. [PubMed: 20207499].
6. Nagai A, Shibamoto Y, Yoshida M, Inoda K, Kikuchi Y. Safety and efficacy of intensity-modulated stereotactic body radiotherapy using helical tomotherapy for lung cancer and lung metastasis. *Biomed Res Int*. 2014;**2014**:473173. doi: 10.1155/2014/473173. [PubMed: 24995299]. [PubMed Central: PMC4065754].
7. Casutt A, Bouchaab H, Beigelman-Aubry C, Bourhis J, Peters S, Lovis A, et al. Stereotactic body radiation therapy with helical-tomotherapy for medical inoperable early stages (I-IIIa) primary and second-primary NSCLC: Outcomes of the one-year experience and analysis of toxicities. *J Nucl Med Radiat Ther*. 2014;**5**(2). doi: 10.4172/2155-9619.1000183.
8. Chen XR, Dong JN, Zhang F, Yao TL. Efficacy and safety of image-guidance radiotherapy by helical tomotherapy in patients with lung cancer. *Medicine (Baltimore)*. 2018;**97**(1). e9243. doi: 10.1097/MD.0000000000009243. [PubMed: 29505510]. [PubMed Central: PMC5943132].
9. Whyte RI, Crownover R, Murphy MJ, Martin DP, Rice TW, DeCamp MM Jr, et al. Stereotactic radiosurgery for lung tumors: Preliminary report of a phase I trial. *Ann Thorac Surg*. 2003;**75**(4):1097–101. doi: 10.1016/s0003-4975(02)04681-7. [PubMed: 12683544].
10. Le QT, Loo BW, Ho A, Cotrutz C, Koong AC, Wakelee H, et al. Results of a phase I dose-escalation study using single-fraction stereotactic radiotherapy for lung tumors. *J Thorac Oncol*. 2006;**1**(8):802–9. [PubMed: 17409963].
11. Jen YM, Lin HH, Su YF, Lin KT, Lin JC, Chang WC, et al. The outcome of cyberknife treatment for primary or metastatic malignant lung tumors. *J Med Sci*. 2014;**34**(4):145. doi: 10.4103/1011-4564.139183.
12. Gibbs IC, Loo BW Jr. Cyberknife stereotactic ablative radiotherapy for lung tumors. *Technol Cancer Res Treat*. 2010;**9**(6):589–96. doi: 10.1177/153303461000900607. [PubMed: 21070081].
13. Nuyttens JJ, Prevost JB, Praag J, Hoogeman M, Van Klaveren RJ, Levendag PC, et al. Lung tumor tracking during stereotactic radiotherapy treatment with the Cyberknife: Marker placement and early results. *Acta Oncol*. 2006;**45**(7):961–5. doi: 10.1080/02841860600902205. [PubMed: 16982564].
14. Brown WT, Wu X, Fowler JF, Garcia S, Fayad F, Amendola BE, et al. Lung metastases treated by Cyberknife image-guided robotic stereotactic radiosurgery at 41 months. *South Med J*. 2008;**101**(4):376–82. doi: 10.1097/SMJ.0b013e318167ad8d. [PubMed: 18360342].
15. [No Author Listed]. *Reports collection of health technology assessment in Iran*. 1st ed. Tehran: Rah of Soraya; 2013.
16. Canadian Agency for Drugs Technologies in Health. Tomotherapy, gamma knife, and cyberknife therapies for patients with tumours of the lung, central nervous system, or intra-abdomen: A systematic review of clinical effectiveness and cost-effectiveness. *CADTH Technol Overv*. 2010;**1**(3). e0119. [PubMed: 22977409]. [PubMed Central: PMC3411154].
17. Kupelian P, Lee S, Lee P, Kamrava M, King C. *Tomotherapy: Accurate treatment with fewer side effects. Department of Radiation Oncology*. Los Angeles, CA: UCLA Medical Plaza; 2018. Available from: www.radonc.ucla.edu.
18. Yang ZX, Shen JT, Li YP, Zhao K, Shi CH, Xiao Y, et al. Helical tomotherapy for cancer treatment: A rapid health technology assessment. *J Evid Based Med*. 2014;**7**(3):192–218. doi: 10.1111/jebm.12109. [PubMed: 25156336].
19. De Bari B, Jumeau R, Bouchaab H, Vallet V, Matzinger O, Troussier I, et al. Efficacy and safety of helical tomotherapy with daily image guidance in anal canal cancer patients. *Acta Oncol*. 2016;**55**(6):767–73. doi: 10.3109/0284186X.2015.1120886. [PubMed: 27034083].

20. Welsh JS, Lock M, Harari PM, Tome WA, Fowler J, Mackie TR, et al. Clinical implementation of adaptive helical tomotherapy: A unique approach to image-guided intensity modulated radiotherapy. *Technol Cancer Res Treat*. 2006;**5**(5):465–79. doi: 10.1177/153303460600500503. [PubMed: 16981789].
21. Boudreau R, Clark M, Nkansah E. *Tomotherapy, gamma knife, and cyberknife therapies for patients with tumours of the lung, central nervous system, or intra-abdomen: A systematic review of clinical effectiveness and cost-effectiveness*. Canadian Agency for Drugs and Technologies in Health; 2009.
22. AHTA. *Tomotherapy HI-ART system radiotherapy planning and treatment for cancer patients*. 2009. 3 p.