Review Article

What is the optimal radiotherapy utilization rate for lung cancer?—a systematic review

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Abstract: Lung cancer is a major cause of morbidity and mortality globally. Although radiotherapy (RT) may be beneficial in the radical and/or palliative management of many lung cancer patients, it is underutilized worldwide. Population-level development of RT resources requires estimates of optimal radiotherapy utilization rates (ORUR) and actual radiotherapy utilization rate (ARUR). A systematic review of PubMed database for English-language articles from January 2009 to January 2019 was performed. Keywords included utilization, underutilization, demand, epidemiologic, benchmark, RT and cancer. Data abstracted included: study population, diagnosis, stage, year of diagnosis, timing of RT, intent of RT, ARUR, and ORUR. Eligible studies provided ARUR or ORUR for lung cancer, small cell lung cancer (SCLC), or non-small cell lung cancer (NSCLC). Included ARUR were based on at least 1,000 patients who were diagnosed or treated in 2009 or later. Included ORUR were based on evidence review or ARUR in 2009 or later. The initial search strategy yielded 1,627 unique abstracts. After review, 105 articles were determined appropriate for full-text review. From these, a final set of 21 articles met all inclusion criteria. In eight papers, ORUR was estimated. Estimated lifetime ORUR ranged from 61% to 82%. Methods for estimation included the evidence-based guideline model, Malthus model, and criterion-based benchmarking (CBB) model. The majority of estimates (6/8) used the evidence-based guideline model. Fifteen papers provided ARUR on lung cancer, inclusive of SCLC and NSCLC. ARUR within 9 months to 1 year of diagnosis ranged from 39% to 46%. Lifetime ARUR was an estimated 52% in Ontario, Canada. Palliative intent ARUR ranged from 12% in Central Poland to 46% in Ontario, Canada. RT is underutilized for lung cancer globally, and there is wide geographical variation in the level of underutilization.

Keywords: Lung neoplasms; radiotherapy (RT); systematic review; global health

Submitted Aug 08, 2019. Accepted for publication Aug 12, 2019.
doi: 10.21037/tlcr.2019.08.12
View this article at: http://dx.doi.org/10.21037/tlcr.2019.08.12

Introduction

Lung cancer has the highest global incidence among cancers excluding nonmelanoma skin cancer and the highest mortality (1). Radiotherapy (RT) is an effective, evidence-based, and guideline-recommended treatment for patients with lung cancer, both for improving outcomes and for palliating symptoms such as shortness of breath, bleeding and pain (2-6). However, RT is underdeveloped and underutilized worldwide, especially in low-and middle-

income countries (LMIC) (7). This has been estimated to cause significant excess morbidity and mortality across a range of cancers, including lung cancer (8).

Expansion of RT resources is complex and costly, but can be cost-effective when planned appropriately (7). Optimal radiotherapy utilization rate (ORUR) and actual radiotherapy utilization rate (ARUR) are common metrics used to forecast such planning. ORUR is the percentage of patients for whom RT is indicated as a treatment option at least once during a time period, and ARUR is the percentage of patients who actually received RT during a time period. The gap between ORUR and ARUR, combined with data on fractionation, retreatment, and incidence for each cancer type, can be used to estimate the unmet demand for RT. In this study, we perform a systematic review of reported ORUR and ARUR for lung cancer.

Methods

A systematic review of the literature was performed per the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines (9). PubMed was searched in January 2019 for articles in English from January 2009 to January 2019. A search strategy was performed using keywords including "utilization", or "underutilization", or "demand", or "epidemiologic", or "benchmark", and "radiotherapy", or "radiation therapy", or "irradiation" or "cancer". Title and abstracts were screened for full-text review independently by W Liu and A Liu, with discrepancies settled by consensus. The bibliographies of identified articles were also searched for potential additional studies. Eligible studies provided ARUR or ORUR for lung cancer, small cell lung cancer (SCLC), or non-small cell lung cancer (NSCLC). Included ARUR were based on at least 1,000 patients who were diagnosed or treated in 2009 or later. Included ORUR were based on evidence review or ARUR in 2009 or later. Full-text review was performed on remaining articles and articles were excluded where appropriate. Data abstracted from the final articles for inclusion included: study details (source of patient data, sample size), patient details (diagnosis, stage, time of diagnosis), treatment details (time of RT, intent of RT, ARUR, and ORUR) and finally methodological details (method used for estimating ORUR). Data abstraction included estimated values from figures where corresponding numerical values were not presented.

Results

The initial search strategy yielded 1,627 unique abstracts. After title and abstract review, 105 articles were determined to be appropriate for a full-text review. From these, a final set of 21 articles met all inclusion criteria and were suitable for data abstraction (*Figure 1*).

Of the eight papers that estimated ORUR for lung cancer (*Table 1*) (7,10-16), six used an evidence-based methodology (7,10-14), one used the Malthus model (15) and one used criterion-based benchmarking (CBB) (16). Two of the six papers that conducted evidence-based estimates of ORUR were performed by the Australian Collaboration for Cancer Outcomes Research and Evaluation (CCORE) group and included systematic reviews of indications for RT (10,11). The remaining four papers were based on the CCORE model and applied different epidemiological data (7,12-14).

Lifetime ORUR for lung cancer were 61% in England using the Malthus model, 62% in Ontario, Canada using CBB, and 77% to 82% using the CCORE evidence-based model. Evidence-based estimates of lifetime ORUR for NSCLC and SCLC were 80% and 59%, respectively (11).

Fifteen papers presented ARUR on lung cancer, SCLC, or NSCLC, including overall ARUR (*Table 2*), palliative intent ARUR (*Table 3*), and curative intent ARUR (*Table 4*) (14,16-29). Measured lifetime ARUR was not available, but lifetime ARUR was estimated using the multicohort utilization table (MCUT) method in Ontario, Canada to be 52% (11). Observation period and method used to calculate ARUR were inconsistent.

Overall ARUR for lung cancer was presented in 6 papers and ranged from 22% in Central Poland to 52% in Ontario, Canada. Overall ARUR for Stage IA NSCLC in the United States of America (USA) increased from 21% in 2009 to 29% in 2012. Overall ARUR for stage I SCLC in the USA ranged from 44% to 53% between 2009 and 2013. Four papers presented palliative intent ARUR ranging from 12% in Central Poland to 47% in Norway. Six papers presented curative intent ARUR on lung cancer, SCLC, or NSCLC. Curative intent RT was variably defined. Curative intent ARUR for stage I SCLC in the USA was 36% to 38%. Stereotactic body radiotherapy (SBRT) use for stage I SCLC in the USA increased from 3% to 6% and conventional external beam radiotherapy (EBRT) decreased between 2009 and 2013 in the USA. For stage I NSCLC, curative intent ARUR was 12% in Europe and England, and 7% to 13% of patients in the USA underwent SBRT.

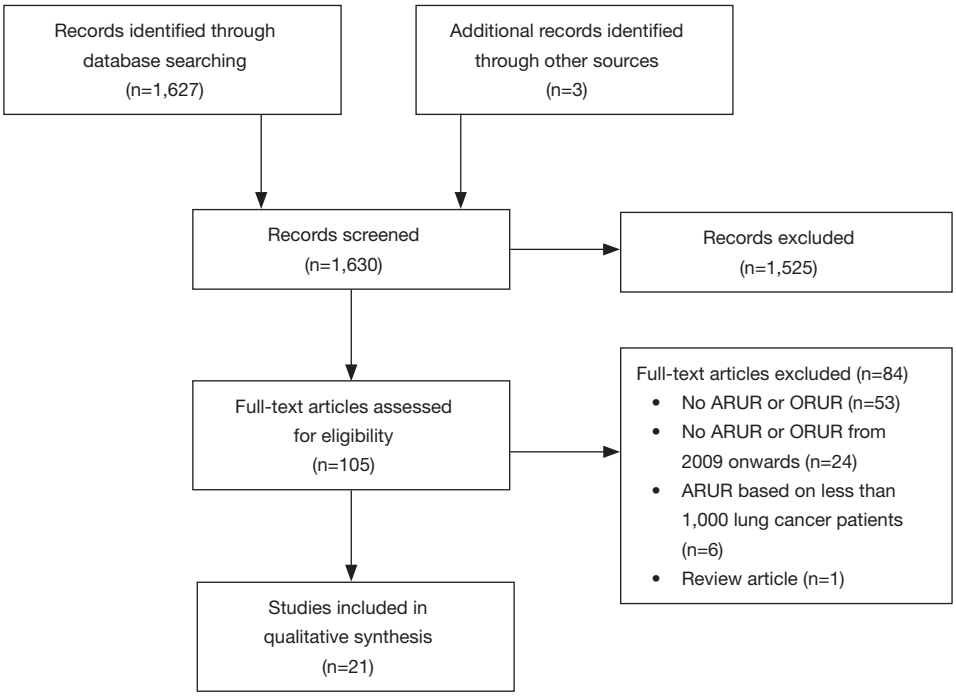

Figure 1 Flow chart of the article search strategy and systematic review process according to PRISMA guidelines. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; ARUR, actual radiotherapy utilization rate; ORUR, optimal radiotherapy utilization rate.

Table 1 Studies reporting ORUR in lung cancer patients

Author [year]	Method used	Cancer Registry	Year of diagnosis	ORUR	Diagnosis	Time of RT	Notes
Barton [2014]	Evidence-based	Australia	2008	77%	Lung cancer	Lifetime	Evidence review performed
Shafiq [2016]	Evidence-based	Australia	2008	77%	Lung cancer	Lifetime	Evidence review performed
				80%	NSCLC		
				59%	SCLC		
Wong [2016]	Evidence-based	Australia	Not reported	78%	Lung cancer	Lifetime	Based on CCORE model (10)
Atun [2015]	Evidence-based	global (GLOBOCAN 2012)	2012	77%	Lung cancer	Lifetime	Based on CCORE model (10)
Borras [2015]	Evidence-based	Belgium	2010–2011	77%	Lung cancer	Lifetime	Based on CCORE model (10)
		Netherlands	2010–2011	78%			
		Greater Poland region, Poland	2010	78%			
		Slovenia	2010	82%			
Lievens [2017]	Evidence-based	Belgium	2009–2010	77%	Lung cancer	Lifetime	Based on CCORE model (10)
Round [2013]	Malthus Model	England	2007–2009	61%	Lung cancer	Lifetime	Evidence review performed
Mackillop [2015]	CBB	Ontario, Canada	2009–2011	54%	Lung cancer	1 year	
				62%		Lifetime	

ORUR, optimal radiotherapy utilization rate; CCORE, Collaboration for Cancer Outcomes Research and Evaluation; CBB, criterion-based benchmarking; NSCLC, non-small cell lung cancer; SCLC, small-cell lung cancer.

Table 2 Studies reporting overall ARUR in lung cancer patients

Author [year]	Diagnosis	Number diagnosed	Cancer registry	Year of diagnosis	Overall ARUR	Time of RT
Asli [2014]	Lung cancer	2,784	Norway	2009	44%	Within 1 year of diagnosis
Chalubinska-Fendler [2015]	Lung cancer	1,307	Central Poland	2009–2012	2009: 24%; 2010: 25%; 2011: 22%; 2012: 27%	2009–2012
Mackillop [2015]	Lung cancer	16,599	Ontario, Canada	November 2009–October 2011	45%	Within 1 year of diagnosis
Lievens [2017]	Lung cancer	14,417	Belgium	2009–2010	39%	Within 9 months of diagnosis
					46%	Within 4–5 years of diagnosis
McLaughlin [2018]	Lung cancer	7,681	Ontario, Canada	January 2011–December 2012	46%	Within 1 year of diagnosis
					52%	Estimated lifetime ARUR using MCUT method
Seo [2018]	Lung cancer	50,384	South Korea	2011–2015	2011: 41%; 2014: 45%	2011–2015
Carrato [2014]	NSCLC	3,508	Prospective study of 182 cancer centres in Belgium, France, Germany, Turkey, Greece, Italy, Portugal and Spain	January–March 2009	Stage I–II: 23%; stage III: 50%; stage IV: 35%; overall: 37%	Followed prospectively for a minimum of 1 year or until death
Haque [2018]	NSCLC, stage IA	15,960	USA (SEER)	2009–2012	2009: 21%; 2010: 23%; 2011: 23%; 2012: 29%. Excludes patients who underwent surgery and RT	2009–2012
Ahmed [2017]	SCLC, stage I	1,902	USA (SEER)	2007–2013	2009: 49%; 2010: 53%; 2011: 47%; 2012: 44%; 2013: 50%	2007–2013

ARUR, actual radiotherapy utilization rate; NSCLC, non-small cell lung cancer; SCLC, small-cell lung cancer; SEER, Surveillance, Epidemiology, and End Results; RT, radiotherapy; MCUT, multicohort utilization table.

Discussion

Lung cancer is the second most common indication for RT globally (7) and has consistently been demonstrated to be the most common indication for palliative RT (18,24,25). In this systematic review, we summarized ARUR and ORUR metrics for lung cancer, and found that lung RT remains underutilized. As lung RT has been demonstrated to be cost-effective (7,30), we would advocate that strategies to optimize its utilization should be prioritized.

Lifetime ORUR for lung RT ranged from 61% to 82%. Evidence-based estimates, the Malthus Model, and CBB are three methods used to estimate lung ORUR, and each has associated strengths and weaknesses. Evidence-based

Table 3 Studies reporting palliative intent ARUR in lung cancer patients

Author [year]	Histology	Number diagnosed	Cancer registry	Year of diagnosis or death	Palliative-intent ARUR	Time of palliative-intent ARUR
Chalubinska-Fendler [2015]	Lung cancer	1,307	Central Poland	Diagnosis: 2009–2012	2009: 16%; 2010: 17%; 2011: 12%; 2012: 12%	2009–2012
Huang [2014]	Lung cancer	2,406	British Columbia, Canada	Death: April 2010–March 2011	46%	Last year of life
					25%	Last 30 days
					12%	Last 14 days
Asli [2018]	Lung cancer	5,260	Norway	Death: July 2009–December 2011	47%	Last 2 years life
Carrato [2014]	NSCLC	3,508	Prospective study of 182 cancer centres in Belgium, France, Germany, Turkey, Greece, Italy, Portugal and Spain	Diagnosis: January–March 2009	Stage I: 6%; stage II: 7%; stage III: 14%; stage IV: 28%; overall: 20%	Followed prospectively for a minimum of 1 year or until death

ARUR, actual radiotherapy utilization rate; NSCLC, non-small cell lung cancer.

estimates are based on a systematic review to determine indications for RT and estimates of the incidence of each indication in a population. Advantages include transparent methodology and the flexibility to adapt the model to different populations and with changes to indications (31). One weakness of the model is reliance on epidemiological data, which may vary in quality. Population-based registries frequently do not include information such as surgical margins, comorbidities and performance status, and this data may be excluded or estimated from less representative sources (31).

The Malthus model uses the evidence-based estimate method and Monte-Carlo simulation. In the one study using Malthus, results were based on local and regional epidemiological data in England. Advantages and disadvantages are mostly consistent with evidence-based estimates. In contrast to the CCORE (Australian) evidence-based estimates, the Malthus model incorporates surgical rates and patient factors such as age, co-morbidities, and preferences (15).

CBB assumes the ORUR to be the ARUR of benchmark populations with optimal access to RT and appropriate decision making. The primary advantage of CBB is that it is based on real-world data. Clinical decisions regarding RT utilization may appropriately deviate from guidelines based on patient factors such as co-morbidities and preferences, and this cannot always be accounted for using other methods to estimate ORUR (32). In the study using CBB with Ontario, Canada data, the benchmark population was identified to be patients diagnosed at cancer centres with an associated RT facility (16). The one-year and lifetime ORUR based on the benchmark population were 54% and 62%, compared to 45% and an estimated 52% in the overall Ontario population. A weakness of this model is that no benchmark population can indeed provide optimal access to RT and decision-making. Additionally, unrecognized barriers to RT may result in underestimation of ORUR, while incentives to provide RT may result in overestimation. Another weakness of CBB is that the estimate cannot be easily modified for changes in indications for RT or epidemiological data.

Additional factors need to be considered from the data presented herein. The Malthus model and CBB produced lower ORUR estimates of 61–62% compared to the CCORE evidence-based estimates of 77–82%, and these were closer to the reported ARURs. One hypothesis for this observed difference may be that patient age, co-morbidities and preferences are reflected in the Malthus model and CBB, but not in the CCORE evidence-based estimates. Lung cancer patients frequently are older, with more co-morbidities and lower performance status. As such, even if RT may be 'indicated', patients may elect not to undergo RT, or referring physicians may deem a patient not eligible for RT (14,32).

ARUR data is limited by the unspecified or short observation period after diagnosis, and inconsistent

Table 4 Studies reporting curative intent ARUR in lung cancer patients

Author [year]	Diagnosis	Number diagnosed	Cancer registry	Year of diagnosis	Curative-intent ARUR	Note	Time of curative-intent ARUR
Chalubinska-Fendler [2015]	Lung cancer	1,307	Central Poland	2009–2012	2009: 13%; 2010: 14%; 2011: 12%; 2012: 15%	–	2009–2012
Møller [2018]	Lung cancer	139,709	England	2010–2013	8%	Radical RT defined as ≥15#	Within 1 year of diagnosis
Stahl [2016]	SCLC, stage I	9,265	USA (NCDB)	2004–2013	2009: SBRT =3%, EBRT =34%; 2010: SBRT =4%, EBRT =34%; 2011: SBRT =4%, EBRT =33%; 2012: SBRT =6%, EBRT =30%; 2013: SBRT =6%, EBRT =30%	ARUR excludes patients who underwent surgery and RT. SBRT defined as BED_{10} 72–300 Gy in <10#. EBRT defined as BED_{10} 30–100 Gy, in 10–45#	2004–2013
Carrato [2014]	NSCLC	3,508	Prospective study of 182 cancer centres in Belgium, France, Germany, Turkey, Greece, Italy, Portugal and Spain	January–March 2009	Stage I: 12%; stage II: 22%; stage III: 33%; stage IV: 6%; overall: 16%	–	Followed prospectively for a minimum of 1 year or until death
Corso [2015]	NSCLC, stage I	113,312	USA (NCDB)	2003–2011	2009: black =7%, white =8%; 2010: black =10%, white =11%; 2011: black =10%, white =13%	ARUR for SBRT, defined as BED_{10} of 70 to 200 Gy, in ≤7#	2003–2011
Brada [2019]	NSCLC, stage I–III	25,659	England	2012–2013	Stages 0–III: 18%; stage 0: 15%; stage I: 12%; stage II: 19%; stage III: 21%	Radical RT defined as >3 Gy/# and dose ≥40 Gy and >10#. OR 1.5–3 Gy/#. OR dose omitted and >20#	2012–2013

ARUR, actual radiotherapy utilization rate; RT, radiotherapy; #, fraction; SCLC, small-cell lung cancer; NCDB, National Cancer Database; SBRT, stereotactic body radiotherapy; BED_{10}, biological effective dose; Gy, Gray; EBRT, external beam radiotherapy; NSCLC, non-small cell lung cancer.

methods used to calculate ARUR (33). However, despite the lack of measured lifetime ARUR, there is clear underutilization of RT for lung cancer. Lifetime ARUR in Ontario, Canada, was estimated using the MCUT method to be 52% (16) and Lievens *et al.* reported 4- to 5-year ARUR of 46% (14), compared to lifetime ORUR of 61% to 82%. One-year ORUR based on CBB was 54% (16), compared to reported one-year ARUR of 44% to 46%. The available 1-year ARUR do not approximate lifetime ARUR, as close to half of patients who die of lung cancer require RT in their last year or two years of life (24,25). Long-term ARUR may be especially important in the era of increasingly effective systemic therapies. As immunotherapy following chemoradiation is now considered the standard of care for unresectable locally advanced NSCLC (34), and as immunotherapy and targeted therapies have resulted in survival improvements in metastatic lung cancer, further research focusing on lifetime ARUR in advanced lung

cancer is warranted.

In addition to research of ARUR in advanced lung cancers, other gaps include the limited information for ARUR in LMICs, where the majority of patients with lung cancer live (35), and in indigenous populations. The majority of existing ARUR and ORUR literature is from North America, Australia or Europe. RT development is crucial in LMICs due to the increased lung cancer mortality (36) and the very limited access to surgery (37) and systemic therapy compared to high-income countries (HIC). While we cannot exclude the possibility that data for LMICs may be available in publications in other languages, another barrier for this type of research is the underdevelopment of population-based cancer registries in some areas. As an example, in Africa, Asia, and Central and South America, 2%, 6% and 8% of the regional populations were included in robust cancer registries, compared to 95% in North America (38). Even within HICs, ARUR data are not available for indigenous populations, who compared to non-indigenous patients from the same country, have increased risk of cancer mortality (39). Further development of cancer registries and calculation of ORUR and ARUR where data are available will allow for more accurate estimation of unmet RT needs.

Conclusions

Based on this systematic review, lifetime ORUR for lung cancer patients ranged from 61% to 82%. ORUR of 61–62% based on CBB and the Malthus model are closer to ARUR compared to evidence-based estimates. Available ARUR data suggest an underutilization of RT in all populations. Almost all data were from North America, Australia, or Europe. No ORUR or ARUR for LMICs were reported.

Acknowledgments

None.

Footnote

Conflicts of Interest: Dr. Louie has received honoraria from Varian Medical Systems Inc. and AstraZeneca. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Liu W, Liu A, Chan J, Boldt RG, Munoz-Schuffenegger P, Louie AV. What is the optimal radiotherapy utilization rate for lung cancer?—a systematic review. Transl Lung Cancer Res 2019;8(Suppl 2):S163-S171. doi: 10.21037/tlcr.2019.08.12

