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Author/s:
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Authors:

Dr. Syed Muntasser Islam[1]

Dr. Shalini K Vinod[2]

Dr. Margot Lehman[3]

Dr. Shankar Siva[4]

Prof. Tomas Kron[5]

Dr. Patrick M Dwyer[6]

Dr. Lois Holloway[7-9]

Dr. Louis Lao[10-12]

Dr. Mei-Ling Yap[9,13-14]

Dr. Jeremy D Ruben[1,15]

1. Radiation Oncology, William Buckland Radiotherapy Centre, Melbourne, Victoria, Australia
2. Cancer Therapy Centre, Liverpool Hospital, Liverpool BC, New South Wales, Australia
3. Radiation Oncology, Princess Alexandra Hospital, Brisbane, Queensland, Australia

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4. Radiation Oncology, Peter MacCallum Cancer Centre, East Melbourne, Victoria, Australia
5. Medical Physics, Peter MacCallum Cancer Centre, East Melbourne, Victoria, Australia
6. North Coast Cancer Institute, Lismore, New South Wales, Australia
7. Medical Physics, Liverpool Hospital, Liverpool BC, New South Wales, Australia
8. South Western Clinical School, University of New South Wales
9. Ingham Institute for Applied Medical Research, Liverpool BC, New South Wales, Australia
10. Radiation Oncology, Auckland City Hospital, Auckland, New Zealand
11. Auckland Radiation Oncology, Auckland, New Zealand
12. University of Auckland, Auckland, New Zealand
13. Radiation Oncology, Liverpool Hospital, Liverpool BC, New South Wales, Australia
14. Radiation Oncology, Macarthur Cancer Therapy Centre, Western Sydney University, Campbelltown, New South Wales, Australia
15. Monash University, Melbourne, Victoria, Australia

Corresponding Author:

Dr. Syed Muntasser Islam

William Buckland Radiotherapy Centre

The Alfred

Commercial Rd

Prahran, 3181

Victoria, Australia

Phone: 03 9076 2000

Fax: 03 9076 2916

Mobile: 04 3333 1985

Email: muntasser@gmail.com

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RADIATION ONCOLOGY ORIGINAL ARTICLE

Abstract

Introduction: The RANZCR Faculty of Radiation Oncology Lung Interest Cooperative (FROLIC) surveyed patterns of lung cancer radiation therapy practice for non-small cell (NSCLC) and small cell lung cancer (SCLC) to evaluate current patterns of care and potential for improvement.

Methods: In October 2014 Radiation Oncologists (ROs) from all 62 departments in Australia and New Zealand were invited to a web-based survey directed at those treating lung cancer. Questions covered current radiation therapy practice as well as quality measures.

Results: Fifty-eight percent of respondents used 4D-CT simulation. For curative treatment, 98% employed 3D-CRT and 34% intensity modulated radiotherapy (IMRT) techniques. Treatment verification was primarily performed using cone-beam CT (86%). In NSCLC, the commonest curative dose-fractionation regime was 60Gy/30# (96%) and for palliative intent, 30Gy/10# (76%). Forty-four percent treated patients with stereotactic ablative body radiotherapy (SABR) and half treated central tumours with this technique. In fit patients with synchronous solitary brain metastases, 80% would give radical treatment. For curative-intent SCLC, 45-50.4Gy/25-28# (61%) and 45Gy/30#/1.5Gy b.d. (48%) were used. Ninety-four percent discussed lung cancer patients at multidisciplinary meetings. Contours were peer-reviewed by 74% and 50% for conventional fractionation and SABR, respectively.

Conclusion: A significant proportion of ROs did not have access to 4D-CT. The majority used 3D image verification and consistently prescribed evidence based doses. A significant number did not participate in peer-review of contours. Practice in IMRT and synchronous oligo-metastatic disease is variable and should be an area of future research. Utilising survey findings, FROLIC is developing consensus recommendations to guide practice.

Keywords: Patterns of Practice, lung cancer, SABR, oligo-metastatic, IMRT, 4D-CT

1 ## Introduction

2 Radiation therapy plays an important role in the management of all stages of lung cancer for both cure and
3 palliation[1]. Despite advances in chemotherapy, surgery and radiation therapy technique, improvements in

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overall survival have been modest. From 1982–1986 to 2007–2011, 5-year relative survival for lung cancer has only improved from 8% to 14%[2]. Lung cancer remains the leading cause of cancer related morbidity and mortality in the Australian population[2]. Despite lung cancer's prevalence and associated mortality rate, prior studies show significant variability in practice[3-4], not only on a national basis, but also within the same state or province.

Detailed surveys specific to Australia and New Zealand lung radiation therapy practice were last conducted in 2007[5]. Since then, technologies in lung cancer radiation therapy have continued to evolve, and there has been increasing adoption of 4-dimensional computed tomography (4D-CT) for tumour motion management and advanced treatment techniques such as Stereotactic Ablative Body Radiotherapy (SABR) and Intensity-modulated radiation therapy (IMRT).

The aim of this study is to evaluate current patterns of care with respect to radiation therapy management of lung cancer throughout Australia and New Zealand in order to highlight areas for future research and quality improvement.

Methods

In October 2014 a web based survey designed using the Surveymonkey® software was developed to understand how Radiation Oncologists (ROs) (both subspecialists and generalists) in Australia and New Zealand manage lung cancer.

To reach the widest possible audience, ROs in all 62 departments from Australia and New Zealand were emailed utilising the RANZCR database, with replies obtained from all states and territories. This data is to date the most complete representation yet of practice in Australia and New Zealand.

There were a total of 36 questions, reviewed by lung cancer subspecialist ROs at the inaugural RANZCR Faculty of Radiation Oncology Lung Interest Cooperative (FROLIC) meeting in September 2014. Questions were designed to obtain information on demographics, simulation techniques, treatment planning, motion management, quality assurance measures, SABR practice, management of oligometastatic disease and small cell lung cancer treatment. The survey was intentionally structured in order to keep average completion time to within 15 minutes, thereby reducing "survey fatigue" whilst maintaining an acceptable completion rate. Question logic software was used to target only ROs who treated lung cancer, and again later in the survey to direct only those who used SABR to an additional set of questions and scenarios relating to SABR.

To protect participant privacy, no department information was collected; however demographic information on State/Territory of practice, rural vs metropolitan and whether the RO was a subspecialist in lung cancer was collected. A subspecialist in lung cancer was defined by FROLIC as any RO with a special interest in treating lung cancer or for whom treating thoracic malignancies constitutes the majority of their practice.

Ethics approval was not required for the study. Responses were collected from 24th October 2014 to 17th November 2014. A descriptive analysis was performed with the results presented as a percentage of evaluable

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responses. If the survey was partially completed, a response was considered evaluable if the question was completed.

Results

Sixty-two responses were received, representing 16% of all Australian and New Zealand ROs registered with the Royal Australian and New Zealand College of Radiologists (RANZCR). Of these, 57 (92%) respondents treated patients with lung cancer and were eligible for analysis.

Forty-five of 57 respondents (79%) answered all questions in the survey. Sixty-one percent of respondents were from metropolitan centres and 39% from regional centres. The demographics of respondents by State/Territory is shown in Fig. 1.

Sixty percent of respondents indicated they were subspecialists in lung cancer. Respondents individually saw a mean of 57 and median of 40 (range 5-200) new lung cancer patients per year. Subspecialists saw a mean of 74 (range 15 – 200) as compared to 30 (range 5-75) for non-subspecialists.

Participation in Trials

Sixty percent of respondents reported they were participating in a lung cancer clinical trial (not specific to radiation therapy). Of the 23 respondents not participating in clinical trials, the key reasons cited were lack of radiation specific trials (38%) lack of trial support staff/infrastructure (25%) or not being equipped for SABR (19%). Nineteen percent of respondents said their research unit was still being set up at the time. Only one respondent (6%) cited lack of funding as a barrier to participation in clinical trials.

Simulation and planning in non-small cell lung cancer

Tumour Motion Management: Radical Intent

ROs were asked to select all options they used in practice for motion management. Fifty-eight percent of respondents used 4D-CT, while 35% used free breathing CT. Positron emission tomography-computed tomography (PET-CT) was commonly used with 23% using PET-CT simulation and 44% PET-CT-fusion. Thirteen percent used gated CT for planning and 12% used peak inspiration and expiration scans. Fluoroscopy was rarely used (2%). One respondent used PET fusion and performed three simulation CT scans, planning treatment using the CT which showed the best correlation of the GTV to the PET scan.

Tumour Motion Management: Palliative Intent

For palliative patients, ROs were asked to select all options they would use for motion management. The vast majority of ROs used free breathing CT (81%). 23% used PET fusion if available and 23% used the same scans as for curative patients.

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68

Respiratory Gating Techniques

Most ROs did not routinely use respiratory gating. Fifty-six percent of respondents had never utilised breath hold or respiratory gating during simulation. Of the 44% who had used it during simulation, 21% regularly used respiratory gating and 9% breath hold. One respondent (2%) used both techniques for all patients.

73

Dose Calculation Algorithms

Curative

Monte Carlo (35%) was the most common dose calculation algorithm used in curative treatments, followed by Anisotropic Analytical Algorithm (Varian Medical Systems, Palo Alto, CA) (27%) and other point kernel dose algorithms (25%) i.e. collapsed cone convolution, CMS XIO (Computerized Medical Systems, USA), Raystation (RaySearch Laboratories, Stockholm, Sweden), convolution and superposition/convolution. Less common responses included "Type B algorithms" which take into account lateral electron dose equilibrium (and would include all the algorithms specified above even if the specific algorithm was not specified).

Palliative

In palliative treatments, respondents largely used the same dose calculation algorithms as selected for curative treatments. However, Monte Carlo was employed less often (25%), so that AAA (27%) and other point kernel techniques (29%) predominated.

Treatment

Treatment Techniques: Curative Intent

ROs were asked what techniques they used to treat patients with curative intent; and allowed to select any that applied. 3D-CRT was used by 98%, with 34% having used IMRT and 18% VMAT. Despite one centre having Cyberknife® available, no respondents reported using this for lung treatment. Two respondents (4%) noted treating patients using helical tomotherapy.

Treatment Verification

ROs were asked which treatment verification techniques they used for curative treatment. The majority utilised 3D cone beam CT (86%) and KV imaging (72%). Thirty percent used MV imaging, 12% used 4D cone beam CT and 6% of respondents used ExacTrac®.

In terms of imaging frequency, 52 % of respondents used daily CBCT (3D or 4D) during treatment. Thirty two percent used a daily CBCT initially on Days 1 to 3-6 then weekly. Only 6% would use daily KV with a weekly CBCT and 4% of respondents would use a 4D-CBCT on day one and then daily CBCT. The remaining 6% stated that their practice varies.

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100 ## Implanted Fiducial Markers

101 No respondents used fiducials during conventional radiation therapy, while 10% would use fiducials during
102 SABR only.

103 ## Lung SABR

104 Forty-four percent of respondents surveyed were treating patients with lung SABR. Respondents were treating
105 a mean of 8 patients (range 0-20) cases per year.

106 ### *Immobilisation during SABR*

107 ROs were asked how they immobilised patients during SABR and allowed to select all options that applied.
108 Sixty-five percent used a vacuum bag/vac-fix cushion. Fifty percent also used a dedicated commercial product.
109 Five percent reported using abdominal compression.

110 ### *Treatment Verification during SABR*

111 ROs were asked to select all treatment verification options they employed for SABR. Seventy-five percent used
112 3D-CBCT and 50% used 4D-CBCT. A smaller number used KV imaging (25%) or Exactrac (15%). All respondents
113 stated that they performed image verification for every SABR fraction, and 60% performed pre, mid and post
114 fraction verification.

115 ### *Peripheral tumours not close to chest wall*

116 ROs were asked to select all dose / fractionation schedules they used for peripheral tumours not close to the
117 chest wall. The most common schedule was 54Gy/3#, employed by 80% of respondents. 30% used 48Gy/4#.
118 The other fractionation schedule used by one respondent was 54Gy/4#.

119 ### *Peripheral tumours close to the chest wall*

120 With tumours close to the chest wall, 70% responded that they would use 48Gy/4#, whilst 20% would use
121 55Gy/5# and 10% would not treat lesions close to the chest wall.

122 ### *Central Tumours*

123 There was significant heterogeneity in practice for central lesions. Fifty percent of respondents would not treat
124 central lesions. Thirty percent would use 60Gy in 8# and 15% prefer 50Gy/5#. One respondent used 18Gy/1#
125 to treat a central lesion. Three respondents wrote that they would only treat the central zone in specific
126 scenarios (avoiding very central/hilar tumours, or only treating on trial).

127 ## Conventional Treatment

128 For conventional curative intent treatment in node positive and node negative NSCLC, dose / fractionation
129 schedules that were employed are shown in Fig. 2 and 3 respectively. Respondents were allowed to choose
130 more than one schedule. In both cases, “Other” responses used doses between 64Gy/32# and 65Gy/35#,
131 while one respondent chose 70Gy/35# in both scenarios.

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Large volume disease precluding radical intent radiation therapy

Significant variation in practice was observed in this area. Schedules employed are outlined in Fig. 4. Respondents were allowed to choose more than one schedule. ''Other'' schedules in use by 22% included 16-17Gy/2#, 36.5Gy/15#, 45Gy/15#, 45Gy/25#, 54Gy/30#, 50Gy/20# and one respondent responded that they would use an "isotoxic regimen".

Oligo-metastatic disease

The survey results show large variations in practice when offering radical treatment to oligo-metastatic sites. We assessed willingness to offer radical treatment using a series of scenarios involving a fit patient of good performance status who had received definitive treatment of the primary tumour.

Brain Metastases

Fig. 5. shows the percentage of respondents willing to treat with radical intent in the setting of a solitary brain metastasis or up to three brain metastases. Respondents were allowed to choose more than one answer.

Systemic Oligo-metastases

For patients with systemic oligo-metastases (eg: adrenal, bone, liver) 35% stated they would offer radical intent treatment to both chest and extrathoracic disease if there was a single systemic metastasis. This reduced markedly to 6.5% for two metastases and 2% for both three to five or fewer metastases. Sixty-one percent stated they do not offer definitive treatment in the setting of systemic oligo-metastases.

Small Cell Lung Cancer

Limited Stage: Curative Intent Fractionation Schedules

Dose / fractionation schedules employed in limited stage SCLC are shown in Fig. 6. Respondents were allowed to choose more than one schedule.

Extensive Stage: Consolidation Chest RT

Sixty-three percent of ROs stated they would give consolidation chest RT for patients who achieved a complete response to chemotherapy at metastatic sites, 48% if a partial response was achieved at metastatic sites and 24% would not routinely give consolidation chest RT in ES-SCLC. Respondents were allowed to choose more than one option for this scenario.

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163 ## Quality Assurance Practices

164 ### *Discussion of new patients at MDT*

165 Ninety four percent of respondents discussed new lung cancer patients at a multidisciplinary team meeting. Of
166 these, 63% responded that they would refer all new lung cases to an MDT, 11% would refer curative cases only
167 and 20% would refer only selected patients. Specific criteria used by ROs to "select" patients was not further
168 elucidated by the survey.

169 ### *Peer Review Meetings*

170 Seventy-four percent of respondents stated that they have a peer review meeting to evaluate lung contours
171 for conventional fractionation in both curative and palliative patients. Most commonly (44%), these meetings
172 were to discuss selected patients (either with curative or palliative intent). For SABR cases, 50% of
173 respondents had a peer review meeting to discuss contours for patients with both curative and palliative
174 intent.

175 ### *Department Protocols*

176 Only 37% of departments had both a dose and contouring protocol for lung cancer. Thirty-nine percent relied
177 on external protocols eg: EviQ[6]. Eleven percent did not have a protocol for contouring or dose prescription.

178 ## Discussion

179 To our knowledge this is the first patterns of practice survey to evaluate the use of new technologies, quality
180 assurance activities, clinical trial participation and management of oligo-metastases in the context of lung
181 cancer. A North American survey of ASTRO members was conducted in 2014[7], however this did not address
182 oligo-metastatic disease or quality control activities, eg: multi-disciplinary tumour board (MDT) participation,
183 contouring guidelines and peer-review.

184 The survey was sent to every Radiation Oncology department in Australia and New Zealand and drew
185 responses from 16% of all ROs. This is a similar response rate to the ASTRO study (20%)[7]. However as
186 respondents were not asked to identify their centre, there may be disproportionately more responses from
187 certain centres.

188 If considering responders from Australia only; 33%, 29% and 21% were from Victoria, NSW and QLD
189 respectively. Comparison using Medicare data[8] of geographic distribution of the Australian Radiation Oncology
190 Workforce for the same states was 30%, 34% and 18% respectively. This suggests responses were fairly
191 distributed by State/Territory.

192 The survey shows that most practitioners follow evidence based practice where evidence exists. This may be
193 affected by resource or patient factors for example in SCLC, where many chose 40Gy/15# once daily rather
194 than a b.d. regimen and in node negative locally advanced NSCLC where many use hypofractionation. It is
195 likely that hypofractionated regimens are used in those of poorer performance status but the question was not

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196 detailed enough to elucidate this with certainty. In keeping with results of RTOG 0617[10], dose escalation
197 beyond 60Gy for locally advanced NSCLC was uncommon.

198 The use of respiratory gating was uncommon and when used, was usually for selected patients only. This
199 reflects uncertainty around the potential benefits of gating, its resource demands and the complexity of its
200 execution[11]. A significant percentage of ROs (42%) did not have access to 4D-CT. In this subgroup, the majority
201 used PET/CT to account for tumour motion. Current Australian lung cancer guidelines recommend either 4D-
202 CT or PET to assess tumour motion[1]. The survey also demonstrates significant uptake of newer radiation
203 therapy techniques such as IMRT (34%) and VMAT (18%) amongst Australia and New Zealand ROs despite the
204 paucity of high-level clinical evidence demonstrating its benefit over 3D-CRT. The current evidence for IMRT in
205 the setting of lung cancer is limited to those retrospective in nature. However a retrospective review from MD
206 Anderson Cancer Centre showed 4DCRT/IMRT resulted in a significant reduction in toxicity (particularly
207 freedom from Grade≥3 radiation pneumonitis) and a significant improvement in overall survival (OS)
208 compared with CT/3D-CRT[12]. As the 3D-CRT arm did not use 4D-CT planning, it is unclear what proportion of
209 this benefit was due to use of the IMRT technique. Conversely, the SEER comparative effectiveness study
210 showed no difference in survival between 3D conformal and IMRT, and no difference in toxicities[13]. These
211 current uncertainties in the evidence have lead to a recent article[14] highlighting the need for prospective
212 comparative studies. When questioned about current gaps in evidence, the survey demonstrated significant
213 interest in evaluating the clinical benefit of IMRT vs 3D-CRT in a trial setting.

214 SABR for early stage lung cancer is widely practised (44%), and there is general consensus on dose for
215 peripheral tumours far from the chest wall (54Gy/3# in 80%) and those close to the chest wall (48Gy/4# in
216 70%). The variety of dose schedules for central tumours reflects the paucity of high level data and variation in
217 published studies. The results of the CHISEL trial[15] are still awaited. The treatment of central tumours is a
218 controversial area. Just half of SABR practitioners were treating central tumours; generally using a risk adapted
219 approach and published regimens[16].

220 The commonest curative regimen for node positive NSCLC was 60Gy in 30 fractions although 30% also used
221 66Gy in 33 fractions. This practice is concordant with results of published studies[17]. Only a single respondent
222 had used 70Gy. For node negative patients with NSCLC, respondents tended to use hypofractionated doses
223 more frequently than for node positive disease. This finding is probably due to smaller and more peripheral
224 planned target volumes (PTV) in node negative disease. Conversely for palliative patients, the wide range of
225 doses employed reflect variables such as performance status and limitations of lung DVHs. A wide range of
226 schedules was used (most commonly 30Gy/10# by 76% and 36Gy/12# by 72%). Thirteen percent of ROs stated
227 they would also treat to higher doses using an isotoxic dose regimen. The survey demonstrates that the use of
228 higher doses to improve local control and survival in better performance status patients is recognised by
229 Australia and New Zealand ROs even when curative intent treatment cannot be given. Most participants
230 nominated more than one potential dose/fractionation regime for the same clinical scenario, reflecting the
231 practice of using "personalised medicine" to tailor the dose based on patient fitness/OAR constraints etc.

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232 Alternatively this could reflect inconsistency in dose prescription or ROs practicing at more than one site with a
233 differing suite of technologies available at each location. This was not further elucidated by the survey

234 Eighty percent of ROs were likely to offer radical intent treatment for a fit patient with solitary brain
235 metastasis and no extrathoracic disease. This is consistent with findings from Flannery et al[18] which showed
236 that median overall survival (OS) for a synchronous solitary brain metastases from NSCLC treated with
237 stereotactic radiosurgery (SRS) was 18 months. A randomized trial (RTOG 95-08[19]) also suggests a functional
238 autonomy benefit to WBRT + SRS, and survival benefit for 1 metastasis.

239 In the presence of up to three brain metastases, 46% of ROs would consider treating the brain definitively. The
240 heterogeneity in answers most likely reflects the absence of high level evidence to show a survival benefit in
241 treating three brain metastases. A recent meta-analysis[20] does suggest a survival benefit in patients aged <50
242 with 1-4 brain metastases, although patients with a single metastasis had significantly better survival than
243 those who had 2-4 metastases. Studies in these patients, to date, have however demonstrated that the
244 addition of a SRS boost to WBRT improves local control and functional autonomy and reduces steroid use[19].
245 Some participants who replied in favour of SRS may have also been influenced by recent randomised evidence
246 demonstrating the negative effect of WBRT on quality of life and cognition[21-22], thus preferring radiosurgery.

247 In contrast to oligometastatic brain disease, the paucity of data for systemic oligometastases is reflected in the
248 low numbers of clinicians who would approach such patients with definitive radiation therapy, especially if
249 multiple oligometastases are present. Active trials are underway such as SABR COMET[23] and SAFRON II[24] that
250 will hopefully provide data in this area.

251 In the setting of extensive stage small cell lung cancer, 24% of ROs did not routinely give consolidation chest
252 radiation therapy. This survey closed prior to publication of the CREST trial[25] (published January 2015) which
253 demonstrated a non-significant hazard ratio for survival although a survival advantage at 2 years (13% vs 3%)
254 and improved progression free survival at 6 months (24% vs 7%) with no severe toxic effects. It will be
255 interesting to see the effect this trial has on future practice.

256 The vast majority of ROs (94%) discuss lung cancer patients at a MDT meeting. Numerous studies show
257 discussing patients at an MDT meeting reduces diagnostic and treatment delays[26-27] and significantly impact on
258 the management plans in 58% of lung cancer patients. There is also evidence that discussion at MDT meeting
259 may also be associated with improved survival[28].

260 Seventy four percent of ROs would discuss conventional fractionation lung contours at a peer review meeting
261 and 50% for SABR. A retrospective study of lung SABR plans recommended minor or major changes in up to
262 two thirds of contoured structures, suggesting peer review resulted in significant changes in lung SABR plans
263 and is warranted to improve consistency and quality of planning[29].

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265 ## Conclusion

266 This survey shows the majority of Australia and New Zealand ROs consistently prescribed evidence based
267 doses and used 3D image verification. A significant proportion of ROs did not have access to 4DCT for
268 simulation. Although protocols were widely used, not every department has their own protocol. There is a
269 need to publish standardised management protocols to guide Australia and New Zealand practice. Almost all
270 patients were discussed at a lung MDT meeting, however a significant number of ROs did not participate in
271 peer review of contours. There is a need to encourage peer review activity. The use of IMRT vs 3D-CRT, the
272 treatment of synchronous oligometastatic disease were variable, likely due to a lack of high quality evidence
273 and should be an area of future research. As a result of findings from this survey, FROLIC is developing
274 consensus recommendations on best practice radiation therapy to complement existing national guidelines[1].

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Figure Legends:

Fig. 1. Demographics of Respondents by State/Territory

Fig. 2. Dose / fractionation schedules used by ROs for curative node positive NSCLC

Fig. 3. Dose / fractionation schedules used by ROs for curative node negative NSCLC

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Fig. 4. Dose / fractionation schedules used by ROs for large volume NSCLC precluding curative radiation therapy

Fig. 5. Percentage of ROs willing to treat a fit patient of good performance status with a solitary brain metastasis or up to three brain metastases with radical intent if receiving definitive treatment to the primary

Fig. 6. Dose / fractionation schedules used by ROs for limited stage SCLC

Figures:

Uploaded separately in individual word documents. Figures created using Microsoft Excel. They have not been submitted as pictures as this would degrade the quality when rescaling.

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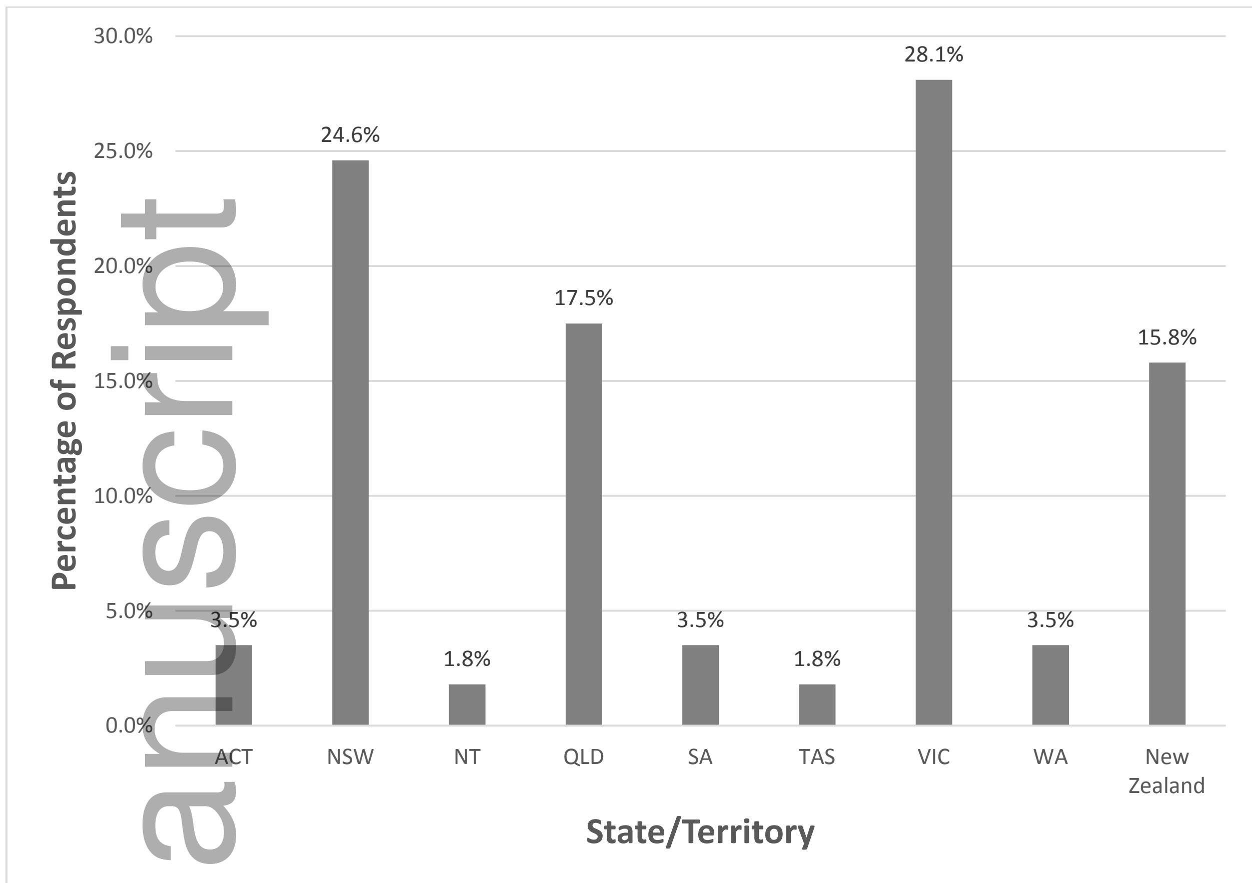

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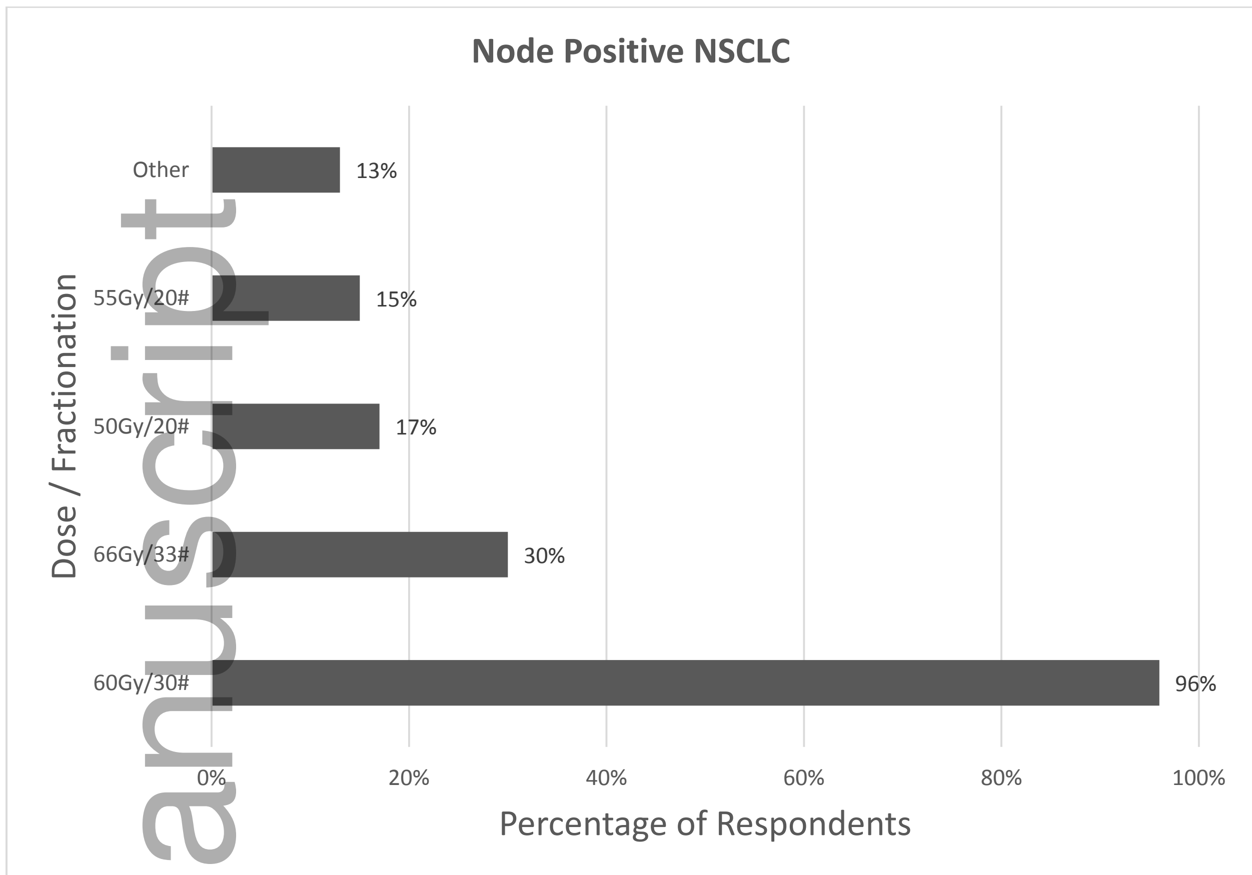

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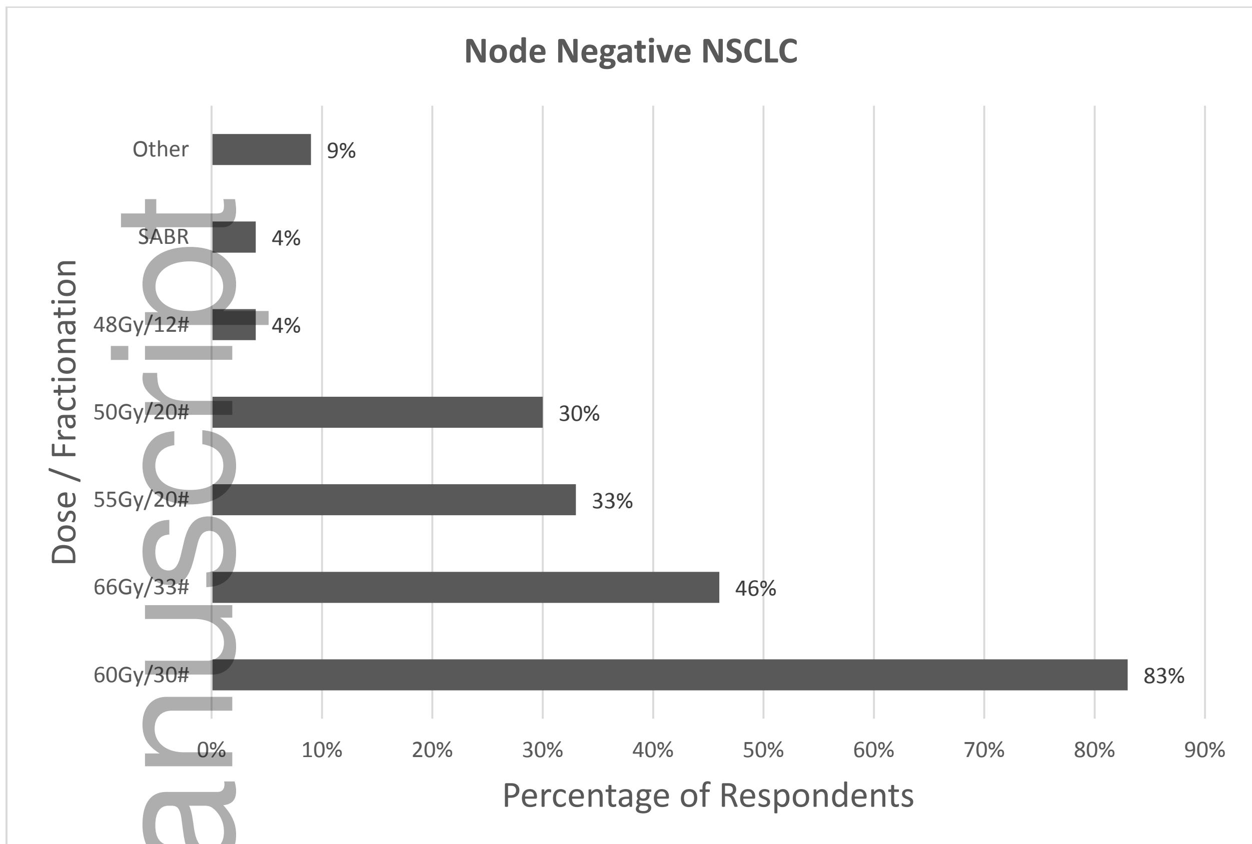

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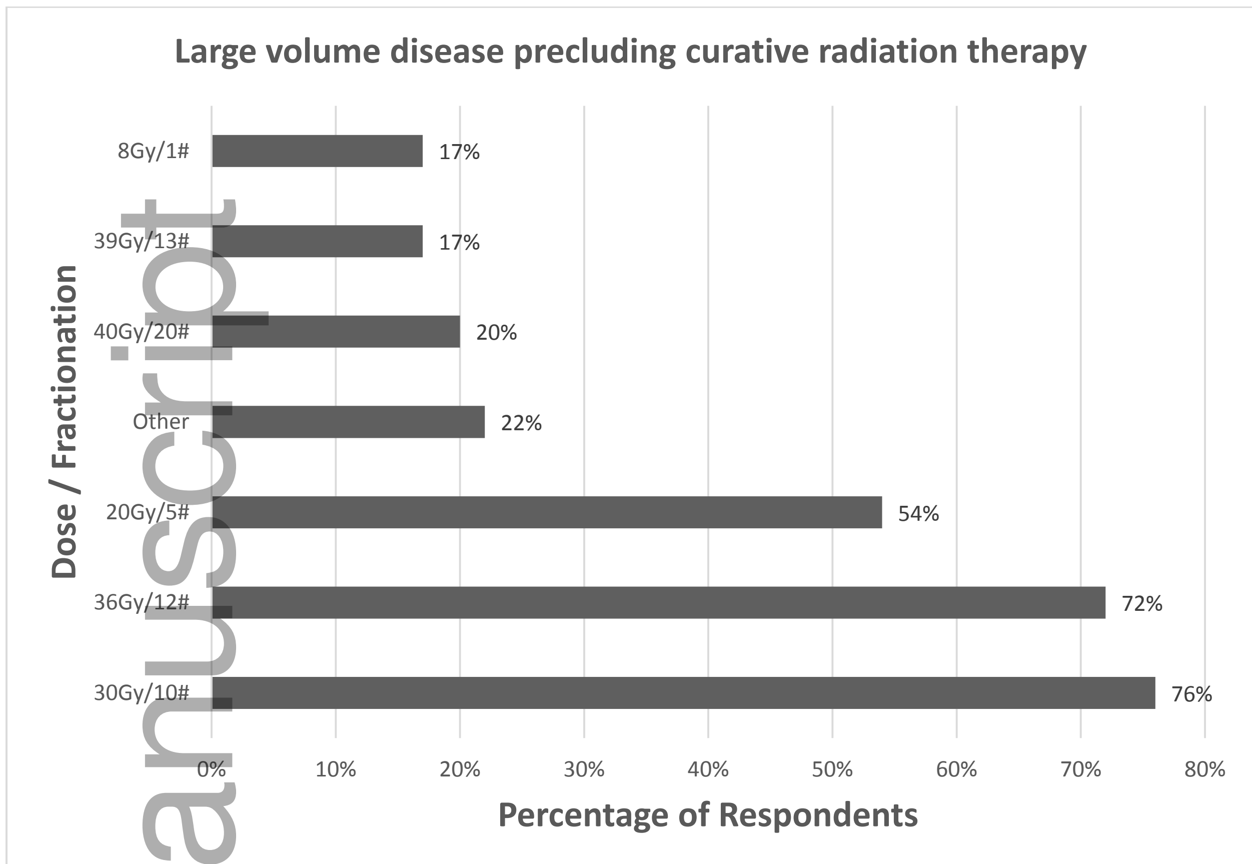

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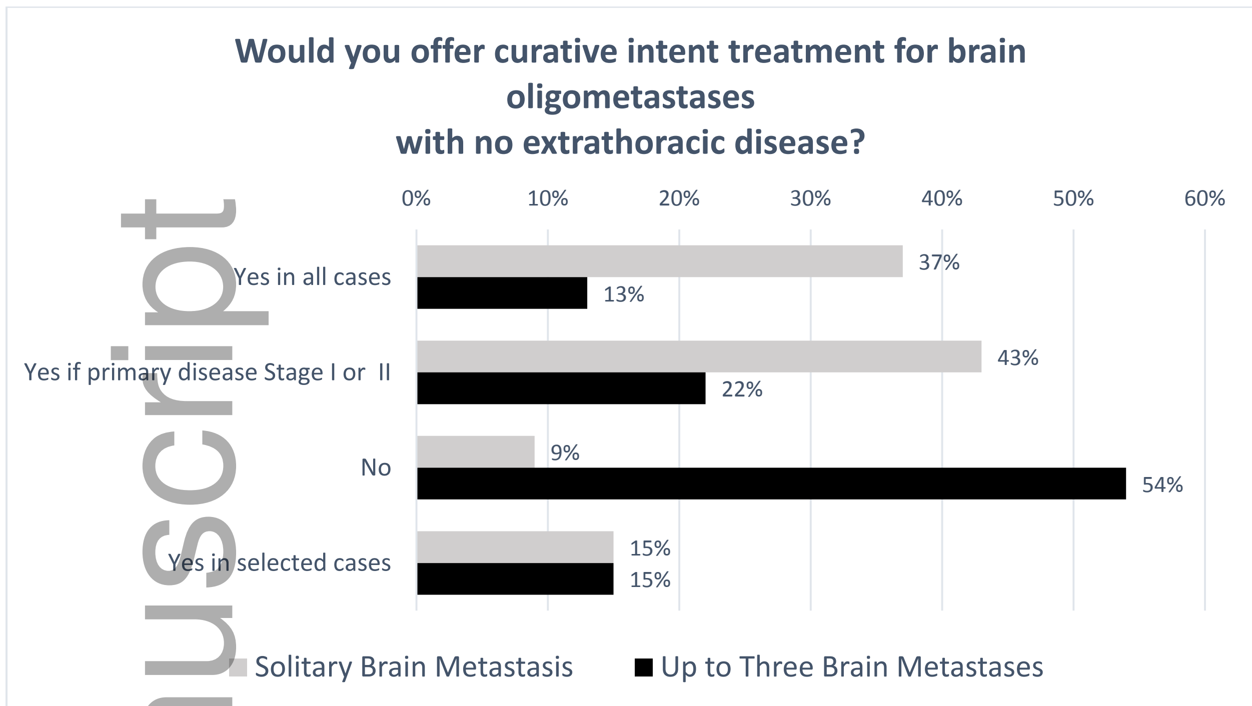

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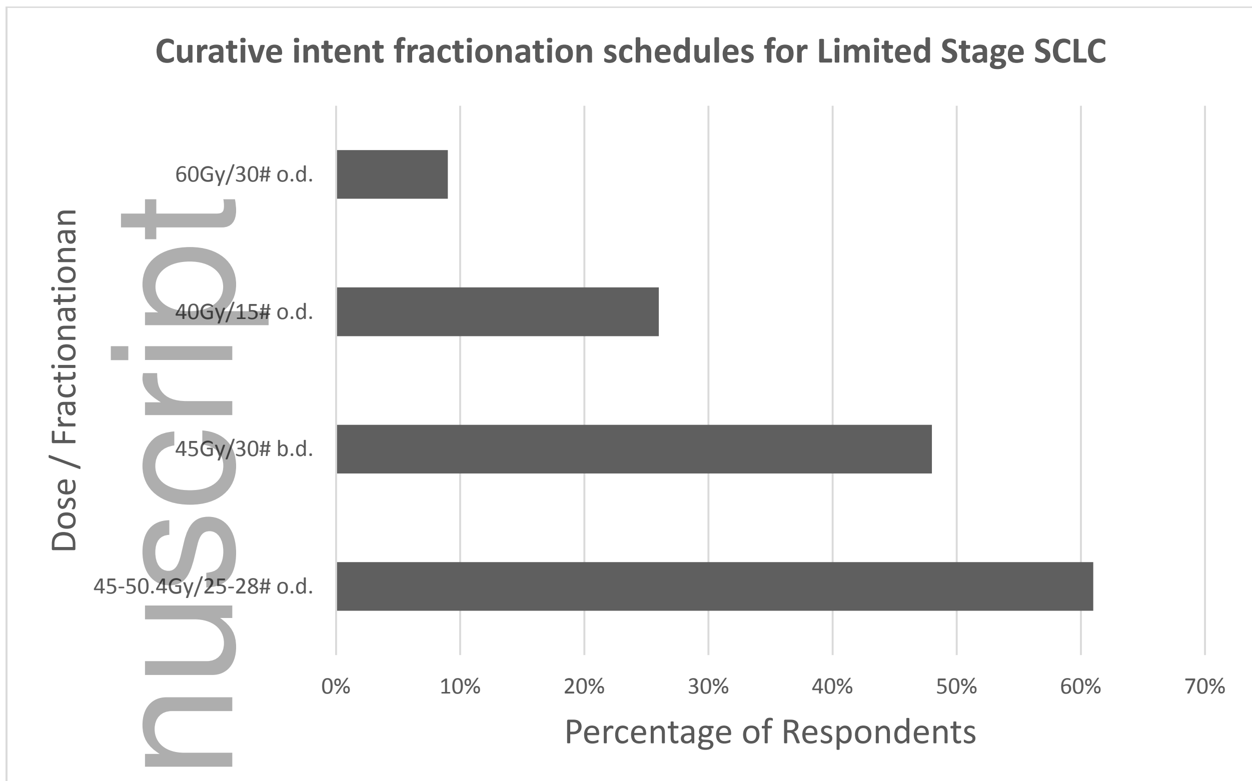

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