Editorial

Adding years to life costs!

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Despite the lack of clear phase-III study data, based on the improvements in progression-free survival (PFS) and overall survival (OS) shown by the phase-II studies, the use of stereotactic body radiation therapy (SBRT) for oligometastatic and oligoprogressive non-small cell lung cancer (NSCLC) is gaining traction (1-3). The addition of therapy usually leads to an increase in the normal tissue and financial toxicity. A lot has been written about financial toxicities especially when patients experience marginal benefit with an expensive therapy producing a low cost-effective ratio. Such studies mostly focus on the direct cost of the therapy and some indirect costs of hospital visits, loss of wages, travel costs, etc. Few studies focus on the costs incurred due to increased hospitalization after treatment or the cost incurred during such hospitalizations. Even though hospitalizations lead to worsening of quality of life, loss of wages, and additional expenditure not only for the patient but also for the caregivers, these are rarely accounted for in the cost-effectiveness analysis.

Lester-Coll *et al.* presented a study using real-world SEER data of treatment trends of metastatic NSCLC patients and showed that the use of SBRT in 1st line significantly increased from 0.5% in 2004 to 3% in 2013 (4). In the study era (2004–2013), stereotactic radiation for extracranial sites was sparingly performed due to the evolving technology, technical expertise, and lack of supporting evidence (5,6). The use was, therefore, limited to patients who were unable to receive standard of care chemotherapy. Additionally, in the absence of known normal organ tolerances to high doses of radiation, patients with small-volume disease were treated with SBRT to minimize the toxicities (7,8). The SBRT cohort in this study classically represents such patients with older median age and greater burden of comorbidities, poor disability status, but lower T and N-stage. Medicare ensured that access to SBRT or chemotherapy was similar across all the median income groups in this study and the choice of therapy was not influenced by patient income (4). All the results should be interpreted with this in perspective. Numerous prospective randomized studies supporting the use of SBRT have been published after the study period augmenting its utilization in not just high but also low and middle-income countries (1,9).

When comparing the hospitalization-associated financial toxicity among different interventions, it is important to not just determine the baseline comorbidities of the patients being studied but to also assess the burden of these diseases. Lester-Coll *et al.* need to be commended for computing the disability status using the out-patient visits and hospital admission in the 2 years preceding the cancer diagnosis and adjusting for this confounder (4). This is critical when the cohort comprises of frail and elderly patients with multiple comorbidities. An improvement shown in survival among unmatched patients treated initially with SBRT by Lester-Coll *et al.* was unsurprising as T and N-stage are strong risk factors and were in favour of the SBRT cohort. However, surprisingly, these patients survived longer even after adjustment for T and N stage (4). SBRT also leads to fewer hospital admissions compared to chemotherapy, after adjusting for age, sex, comorbidity, and disability status.

Apart from the rate of hospitalization, the length of stay and the cost of in-patient treatment, and the outcome of hospitalization can greatly impact the quality of life and can influence the decision-making when multiple treatment

options with similar outcomes are available (10). For example, patients may prefer chemotherapy over radiation therapy if it results in a relatively more frequent but short duration stay for non-life-threatening febrile neutropenia over a less frequent but prolonged stay for the treatment of life-threatening radiation-induced pneumonitis. Lester-Coll *et al.* showed that these patients get admitted on an average 2–3 times in their remaining life; 16–17 days post-SBRT and 13–14 days after chemotherapy (4). Even though SBRT lead to longer hospitalizations, after matching for confounders, initial SBRT compared to chemotherapy lead to a fewer number of hospital admissions (4).

As per the Centers for Disease Control and Prevention, the average length of hospital stays steadily declined from 1980 and in 2004, it was 5.4–5.8 days for patients ≥65 years (11). However, in the subsequent years from 2005 to 2014 as per the Healthcare Cost and Utilization Project, the number of inpatient stays increased by 8.5% in this age group leading to an inflation-adjusted increase in cost by 10.5% (12). After adjusting for the increase in population size, the population rate of inpatient stays in the same age group declined by >20%. After excluding pregnancy and neonatal admissions, in 2005, the most common admitting diagnosis was pneumonia and in 2014 it was septicaemia (12). For patients ≥65 years of age, Septicaemia and Pneumonia were among the top 5 admitting diagnosis (12). The mean cost per stay in this age group in 2014 was $13,150 (12). Therefore, hospital admission after SBRT ($13,647) was still costlier by $497 whereas it was cheaper after chemotherapy ($10,432) by $2,718. This cost difference can be due to additional 3.2 days of hospitalizations post-SBRT and the difference in the type of care required for the admitting diagnosis. It is noteworthy that patients in this age-group undergo frequent hospitalizations for pneumonia and septicaemia and all admissions captured can't be attributed to either SBRT or chemotherapy based on limited SEER data. Nevertheless, Lester-Coll *et al.* showed that this increase in hospitalization cost after SBRT was offset by improved survival, ultimately leading to no significant difference in cost incurred per survived month after SBRT or chemotherapy (4).

Two phase-II randomized controlled trials (RCTs) in oligometastatic NSCLC evaluating the role of local ablative therapies have been published recently and demonstrated significant improvement in PFS (1,9). Gomez *et al.* reported long-term outcomes after a median follow-up of 38.8 months in favour of local consolidative therapy with an improvement of 10 months in median PFS (14.2 *vs.* 4.4 months, P=0.02) and 24 months in mOS (41.2 *vs.* 17.0 months, P=0.017) (3). Similarly, Iyengar *et al.* demonstrated a significant benefit in PFS of 9.7 months with SBRT *vs.* 3.5 months for maintenance (P=0.01) (1). Both studies reported that SBRT was safe and effective with no additional grade >3 toxicities when SBRT was combined with systemic therapy. Treatment for metastatic NSCLC has undergone a paradigm shift with newer tyrosine-kinase inhibitors and immunotherapy. Immunotherapy either as monotherapy or in combination with other immune checkpoint blocker or chemotherapy is approved as 1st line therapy for patients without targetable mutation as it leads to improved PFS and OS (13). Furthermore, SBRT to oligometastatic sites prior to immunotherapy has shown to further improve the overall response rates (from 18% to 36%) and this strategy is being studied in several clinical trials (2,13). The encouraging results promise that such combinations would be explored in the future and hospitalization rates among this cohort may be noteworthy.

Future studies should focus on studying such cohorts prospectively for identifying determinants of prolonged stay. Lung cancer patients who are tobacco smokers or those with prolonged exposure to smoke suffer from chronic obstructive pulmonary disease (COPD) (14). Unplanned, emergency, and re-hospitalizations are not uncommon among COPD patients. Special COPD case management programs where dedicated teams identify, follow, and develop comprehensive care plans for such patients and perform home visits to improve therapy adherence have shown to reduce hospitalization rates and length of stay (15). Since Lester-Coll *et al.* excluded patients specifically enrolled with Health Maintenance Organization, these patients were unlikely to be enrolled in such intense management programs. Such programs can potentially reduce the global healthcare burden and penalties by the US Centers for Medicare & Medicaid Services because of hospitalizations. While grade >2 SBRT toxicities are few they can be further reduced using modern treatment planning, motion management techniques, and identifying predictors of toxicity (14). Additionally, bringing automation in treatment planning and delivery processes can help to reduce the cost of SBRT ultimately making it more cost-effective (16). Similarly, using less toxic but more effective 'generic' immunotherapy can make initial systemic therapy more accessible and cost-effective like SBRT.

Despite several limitations of SEER Medicare data, important findings emerge from this study viz., 2–3 episodes of prolonged hospitalizations are common among elderly,

metastatic lung cancer patients with comorbidities. Initial therapy may influence the admitting diagnosis, length, and cost incurred during hospitalization. Efforts should be focused on reducing the cost of treatments, acute and late toxicities, and consequential hospitalizations associated with newer treatments in metastatic and advanced lung cancer patients. Concerted global efforts are needed to decrease the ever-mounting healthcare burden such that adding years to life wouldn't be so costly.

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