Review Article

Is immunotherapy at reduced dose and radiotherapy for older patients with locally advanced non-small lung cancer feasible?—a narrative review by the international geriatric radiotherapy group

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Background and Objective The standard of care for locally advanced non-small cell lung cancer (NSCLC) is either surgery followed by adjuvant chemotherapy with or without radiotherapy or concurrent chemotherapy and radiotherapy. However, older patients (70 years old or above) with multiple co-morbidities may not be able to tolerate the combined treatment due to its toxicity. Since lung cancer prevalence increases significantly with age, a new algorithm needs to be investigated to allow curative treatment for those with locally advanced disease.

Methods: A literature search of the literature was conducted through PubMed and Google Scholar using search terms such as locally advanced NSCLC, older cancer patients, immunotherapy with check point inhibitors (CPI), and image-guided radiotherapy (IGRT). Abstracts were screened, full articles fitting the article topic were reviewed, and duplicated and non-English articles were excluded.

Key Content and Findings: Recently, CPI has been introduced and proven effective for selected patients with increased program death ligand 1 (PD-L1) expression (50% or above). A reduced dose for CPI (RDCPI) may be as effective as a full dose and may decrease treatment cost. New radiation technique such as IGRT may also minimize radiotherapy complication through normal lung and cardiac sparing.

Conclusions: IGRT and RDCPI may be an innovative option for older patients with locally advanced NSCLC and high PD-L1 expression and needs to be investigated in future prospective studies.

Keywords: Older; cancer patients; locally advanced; reduced dose for check point inhibitor (RDCPI); image-guided radiotherapy (IGRT)

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Introduction

Lung cancer prevalence increases significantly with age. According to the American Cancer Society (ACS), most lung cancer occur in people 65 years old or above. The mean age at diagnosis for lung cancer is 70 (1). Among all cancers in men and women, lung cancer is most prevalent in individuals aged 85 and above and the leading cause of death in that population (2). In patients with locally advanced non-small cell lung cancer (NSCLC), recommended standard of care is concurrent chemotherapy and radiotherapy or surgery followed by adjuvant chemotherapy with or without radiotherapy (3). Concurrent chemoradiation is advocated over radiotherapy alone for stage III NSCLC because of its radiosensitizing effect and improved survival. However, grade 3–4 toxicity is also significantly increased and may not be suitable for frail patients. Surgery may not be an option for those patients because of pre-existing comorbidity and high mortality rate (4,5). In fact, older age by itself is the strongest predictor of non-treatment. Only 70% of lung cancer patients aged 75 or above received any type of treatment despite the fact that they had no comorbidity (6). In another study of 12,641 NSCLC aged 80 or above presenting with stage III disease at diagnosis, 7,921 (62.7%) did not receive treatment (7). Clinicians are traditionally reluctant to treat older lung cancer patients because of concern for toxicity and the lack of supportive data (8). Older patients with lung cancer are less likely to receive surgery, chemotherapy, and radiotherapy compared with younger ones (9). The probability of receiving curative treatment for lung cancer decreases significantly with older age (10). Thus. a new treatment strategy needs to be implemented to decrease treatment toxicity and to allay clinician anxiety as older lung cancer patients are frequently excluded from clinical trials (11,12).

An ideal treatment modality should involve a systemic agent that has been proven effective based on tumor biomarkers, less toxic compared with traditional chemotherapy and combined with a radiotherapy technique that minimizes irradiation to the organs at risk (OAR) surrounding the tumor. The chosen systemic agent should also act as radiosensitizer to improve local control. Among those agents, immunotherapy with check point inhibitors (CPI) is a promising therapy for tumors that carry program death ligand 1 (PD-L1) receptors (13). CPIs have been proven to be superior to chemotherapy among metastatic NSCLC patients with a high tumor proportion score (TPS) defined as PD-L1 50% or above (13). Meta-analysis of randomized CPI studies reports less treatment discontinuation and grade 3–5 toxicity compared with chemotherapy (14). Analysis of randomized studies for patients with NSCLC demonstrated that immunotherapy is very well tolerated among older patients and is as effective compared with younger patients (15). Thus, based on those studies, CPI may be ideally suited for locally NSCLC in the geriatric population. On the other hand, among the innovative techniques of radiotherapy, image-guided radiotherapy (IGRT) allows precise targeting of the lung tumor despite the tumor motion with respiration (16). Radiation dose escalation of 7,000–7,500 cGy to the gross tumor has been reported to be feasible without excessive cardiac or lung complication (17).

Thus, the combination of CPI and IGRT may allow improve tolerance of older patients with locally advanced NSCLC for curative treatment and is the subject of this investigation. We present the following article in accordance with the Narrative Review reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-821/rc).

Methods

A literature search was conducted through PubMed and Google Scholar from January 1969 to February 2022 using search terms: locally advanced NSCLC, older cancer patients, immunotherapy with CPI, and IGRT. Articles fitting the topic of this review were fully reviewed. Duplicate articles and the ones published in the non-English language were excluded. The first-time screening requires comprehensive understanding of the titles and abstracts. A total of 5,700 abstracts were identified independently by three authors familiar with geriatric medicine, lung cancer, immunotherapy, and IGRT; 529 articles were fully reviewed; 32 were excluded as duplicated. After further consultation with a pharmacologist familiar with pharmacokinetics in older patients to identify key articles, 88 articles were selected for this review. *Table 1* summarizes the search strategy.

Discussion

Prevalence of PD-L1 receptors in locally advanced NSCLC

The efficacy of CPI is correlated to the percentage of PD-L1 expressed in tumor cells. Those with high TPS usually respond well to CPI administration. The prevalence of

Table 1 The search strategy summary

Items	Specification
Date of search	September 2021 through February 2022
Databases and other sources selected	PubMed and Google Scholar
Search terms used	locally advanced NSCLC, older cancer patients, immunotherapy with CPI, IGRT
Time frame	January 1969 to February 2022
Inclusion and exclusion criteria	English articles only, duplicates excluded
Selection process	Three independent investigators familiar with geriatric medicine, lung cancer, immunotherapy, and IGRT
	Consultation with a pharmacologist familiar with pharmacokinetics in older cancer patients following initial screening process to identify key articles

NSCLC, non-small cell lung cancer; CPI, check point inhibitor; IGRT, image-guided radiotherapy.

tumors with a high TPS score ranged from 10.5% to 31% for locally advanced NSCLC (18-27). There was no difference in high TPS expression between younger and older patients. Thus, a significant percentage of older patients may benefit from immunotherapy with CPI.

Potential advantage of CPI over chemotherapy in older patients with locally advanced NSCLC

Anemia is frequently observed among older patients. Its etiology is complex and reflects a combination of reduced renal function, chronic inflammation, nutritional deficiency, reduced erythropoietin production, and other co-morbidity (28). Older patients may not tolerate chemotherapy very well and may require dose reduction because of severe toxicity (29). Patients who are frail and have underlying co-morbidity are particularly prone to severe chemotherapy complications (30). Even though immunotherapy with CPI may also lead to hematologic toxicity, randomized studies of CPI in NSCLC reported a significant reduction in severe toxicity in comparison with chemotherapy: grade 3–5 toxicity was 13.8% and 39.8% for CPI and chemotherapy respectively (14). There was also less treatment discontinuation among patients who received CPI. Immunotherapy with CPI is very well tolerated among older patients. In a retrospective review of 290 patients with NSCLC treated with CPI, there was no difference to toxicity among patients aged 70 years old or less, 70–79, and 80 or above (31). The safety of CPI for older patients with NSCLC is also corroborated in other studies where patients were treated outside of a clinical trial (32-34). There is no difference in toxicity and response rates between younger and older patients. The response rates are also similar to the ones reported in clinical trials (32,33). In addition, among phase I–II clinical trials with CPI for solid tumors, older age did not lead to dose reduction, decreased efficacy, or increased grade 3–4 toxicity (35). The safety and efficacy of CPI for older patients is further corroborated through a multi-institution study of 448 patients not only for lung cancer but also for other solid tumors such as melanoma or renal cell cancer (36). Taken together, those studies suggest that CPI may be ideal systemic agents for older patients with NSCLC due to their safety profile.

Furthermore, in combination with radiotherapy, CPI may have improved efficacy because of the synergy between radiotherapy and immunotherapy. Radiotherapy alone or combined with chemotherapy induce tumor antigen release and an adaptive immune response (37-40). However, radiotherapy may increase the risk of pneumonitis of immunotherapy. Thus, a radiotherapy technique that allows radiotherapy dose escalation without excessive normal lung and cardiac irradiation is needed to reduce the risk of grade 3–4 pneumonitis and myocarditis.

Potential of IGRT in locally advanced NSCLC for normal organs sparing

Technical advance in radiotherapy such as intensity-modulated radiotherapy (IMRT) allows sparing of the normal organs such as the lung and heart from excessive radiation due to the steep dose gradient away from the target. In a randomized study of dose escalation comparing conventional three-dimensional conformal radiotherapy (3D-CRT) to IMRT for locally advanced NSCLC, IMRT

produced significant heart and lung sparing despite a larger target volume (41). Thus, lower rates of grade 3–4 pneumonitis was observed in the IMRT arm (41).

In addition, IMRT based IGRT has been introduced to target the gross tumor volume and involved mediastinal lymph nodes accurately while taking into consideration tumor motion with respiration. Advances in imaging such as positron emission tomography (PET) allows the clinician to outline the target more precisely for radiotherapy planning. Daily imaging prior to irradiation with cone beam CT (CBCT) scan for example also ensures accurate tumor targeting to minimize marginal miss and sparing of critical organs surrounding the target. Thus, radiation dose escalation to the tumor becomes feasible while minimizing radiation dose to the heart and lungs. Preliminary experience has been promising (17,42,43). In a study of 169 patients with locally advanced NSCLC treated with concurrent chemoradiation, those treated with IGRT (n=62) had improved loco-regional control compared with the ones without. Local control was respectively 80% and 64% for IGRT and non-IGRT technique (43). Radiation dose escalation was also feasible without increased grade 3–4 toxicity despite the radiosensitization effect of chemotherapy (17). Many techniques of IGRT with or without fiducial markers have been implemented successfully (44,45). Imaging studies performed daily before irradiation using CBCT either with kilovoltage (KV) or megavoltage (MV) X-rays for imaging, magnetic resonance imaging (MRI) or fiducial markers takes into consideration the tumor movement with respiration to target the tumor precisely (44). Adaptive therapy may also be implemented if there is significant decrease of the tumor volume during treatment and may allow optimization of radiation dose around the target (46). Taken together, technical advances in radiotherapy lead to improved local control and reduced treatment toxicity for lung cancer. Even though IGRT has not been investigated with immunotherapy for locally advanced NSCLC, this combination may be intriguing to improve survival due to the high risk of loco-regional failures and distant metastases treated with conventional chemotherapy and radiotherapy (47).

Effectiveness of CPI in patients with advanced NSCLC

Many randomized studies have demonstrated the superiority of various CPI over conventional chemotherapy in advanced NSCLC (48-50). In a study of 272 patients with advanced squamous cell lung cancer who experienced disease progression during or after first line chemotherapy, overall survival rates at 1 year were 42% and 24% for nivolumab and docetaxel respectively (48). Grade 3–4 toxicity was also significantly reduced for nivolumab (7%) compared to docetaxel (55%). The efficacy and safety of CPI for patients with NSCLC with disease progression following previous chemotherapy was also corroborated in another study: median survival was 15.7 and 10.3 months for atezolizumab (n=425) and docetaxel (n=425), respectively (49). A significant reduction in grade 3–4 toxicity was also observed for atezolizumab (15%) versus docetaxel (43%). Thus, CPI are effective in improving survival and decreasing serious toxicity for patients who failed previous chemotherapy.

Among patients with advanced NSCLC who were chemotherapy naïve, the combination of nivolumab and ipilimumab is proven superior to platinum-doublet chemotherapy irrespective of PD-L1 expression (50). Among patients with PD-L1 1% or more, the 2-year survival was 40% and 33% for CPI and chemotherapy, respectively. For patients with PD-L1 expression less than 1%, the 2-year survival was respectively 40% and 23% for CPI and chemotherapy.

There was no difference in grade 3–4 toxicity between the two groups which was reported to be 32% and 36% for CPI and chemotherapy. Duration of response was also longer with CPI (23.2 months) compared with chemotherapy (6.2 months).

In another study of chemotherapy naïve patients with advanced NSCLC who had high TPS without epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) translocation, pembrolizumab was associated with better survival compared to platinum chemotherapy and less grade 3–5 toxicity (51). Median survival was 30 and 14.2 months for pembrolizumab and chemotherapy, respectively. Grade 3–5 toxicity was respectively 31.2% and 53.3% for pembrolizumab and chemotherapy.

Taken together, those studies suggest that for selected NSCLC patients with high TPS, CPI may be more effective and less toxic compared with conventional chemotherapy. It is also reassuring that the efficacy and toxicity profile of CPI is similar among older and younger patients in those studies. Interestingly, in metastatic NSCLC patients with disease progression following chemotherapy alone or combined with ipilimumab, high dose of radiotherapy (5 times 600 or 900 cGy) in combination with ipilimumab induced tumor response (52). Thus, high dose of radiotherapy may be used in synergy with CPI to overcome tumor resistance to CPI

alone.

In a review of 90 patients with solid tumors treated with escalating dose of CPI in phase I study, the severity of side effects was related to dose. The prevalence of side effects was 6%, 10%, 17%, and 29% for low dose, medium dose, high dose, and very high dose, respectively (53). There was no difference in survival or progression-free survival between low dose or very high dose of CPI. Even though this is a phase I study with its limitations, the study suggested that immunotherapy dose reduction may improve treatment tolerance and may serve as a template for future prospective studies. In another study of ipilimumab for metastatic melanoma, prevalence of any side effects was 70.4%, 64.7%, and 26.3% for doses of 10, 3, and 0.3 mg/kg respectively (54). The most serious side effects occurred in the group receiving 10 mg/kg while the lowest dose group had no grade 3–4 side effects. However, there is still controversy about the role of body mass index (BMI) in CPI's toxicity which needs to be investigated in the future for each individual agent (55-59).

Pharmacokinetic of CPI

CPIs are humanized or human immunoglobulin (Ig) G1 (anti PD-L1) or G4 (anti PD-1) with a long half-life. Following binding of the Ig G to the specific receptors, it undergoes elimination through lysosomal degradation to amino acids through a receptor-mediated endocytosis process (60). Due to the high affinity of the Ig G to the specific receptor target, a significant portion of the Ig dose will be sequestered by the target at low dose (non-linear pharmacokinetic). However, as Ig G dose increases, due to target saturation, its elimination becomes proportional to the dose given (linear pharmacokinetics). The antibody will be catabolized through non-specific endothelial pinocytosis (61). Clearance of the antibody is a complex process depending on sex, body weight, tumor burden, tumor type, albumin, and immunogenicity (62). Low clearance of CPI has been reported to improved response rate and survival (63). As CPI clearance may decrease over time with repeated administration, one can postulate that a reduced CPI dose and/or administered at extended interval may be effective to saturate the receptors and maintain the drug efficacy (64,65). Indeed, for pembrolizumab for example, one of the most accurate measures of its efficacy is the production of interleukin-2 (IL-2) by T cells when pembrolizumab binds to their PD-1 receptors. There was no difference in IL-2 levels with pembrolizumab dose of 1, 3, and 10 mg/kg suggesting that the receptors are already saturated at lower pembrolizumab dose (66) for Such a policy may also reduce treatment cost as CPI are expensive and may also improve patient quality of life will less visit to treatment centers. Older cancer patients have limited mobility and have been reported to experience transportation barriers which limit their participation in clinical trials (67).

Is CPI dose reduction (RDCPI) an option for older NSCLC with locally advanced disease?

Preliminary clinical data suggests that CPI dose may be adjusted without a change of its efficacy. A study of 137 patients with lung cancer and melanoma reported that there was no difference in survival or toxicity between a flat dose nivolumab and pembrolizumab compared with a weight-based dose (68). The weight-based dose was more cost effective leading to a saving of $1,820.46 per patient per course of treatment and a total saving of $642,877 over all courses of therapy (68). In another study, among 129 patients with NSCLC, response rate was 24% and 20% for nivolumab dose of 3 and 10 mg/kg, respectively (69). There was also no difference in grade 3–4 side effects between those two levels. Effective low dose nivolumab for NSCLC was also corroborated in another study. Among 47 patients with advanced or metastatic NSCLC, 18 received low dose nivolumab (20 or 100 mg fixed dose every three weeks) and 29 had the higher standard dose (3 mg/kg every two weeks). The response rate was 16.7% and 13.8% for the low dose and standard dose, respectively (70). There was also no difference in survival between those two groups.

Taken together, those studies suggested that dose reduction and/or interval extension of CPI may be feasible for locally advanced NSCLC especially for patients with high TPS expression and needs to be investigated for older cancer patients in future clinical trials. Interval extension of CPI is particularly attractive in view of the long half-life of nivolumab (25 days) and pembrolizumab (23 days) (71). The high affinity for CPI for PD-1 receptors at very low dose ranging from 0.1–0.3 mg/kg for nivolumab is also another strong argument for the extended regimen (72). As an illustration, among 150 patients with advanced NSCLC, 92 received pembrolizumab at extended intervals (more than three weeks) for various reasons and 58 had the standard regimen (every three weeks). There was no difference in survival or disease-free survival between those two groups (73). Thus, in theory, one could consider for

example, pembrolizumab every six weeks in combination with hypofractionated IGRT for older cancer patients with locally advanced NSCLC to minimize transportation issue and to decrease treatment cost. Another study reported that there was no difference in disease progression between patients who received a standard dose of nivolumab (3 mg/kg every two weeks) versus a non-standard dose (3 mg/kg every three to eight weeks) for NSCLC (74). Those studies are retrospective and include small number of patients. However, they raised the interesting question that RDCPI may be an option for selected patients with NSCLC. Preliminary data also suggested that older cancer patients tolerated single-agent CPIs very well. However, for those who are 90 years or older, there were significant treatment disruptions because of increased toxicity (75). Thus, RDCPI may be an attractive option for those patients.

As hypofractionated IGRT may also reduce treatment toxicity and time, this schedule is particularly fit for older cancer patients. Hypofractionated radiotherapy consists of the delivery of a large dose radiotherapy once a day (more than 200 cGy) or less often compared to a standard dose of radiotherapy which ranges from 180 to 200 cGy. Thus, overall treatment time can be shortened from a week to two weeks compared to six to seven weeks with the conventional fractionation. Many schedules of radiotherapy have been adopted for stereotactic body radiotherapy (SBRT) for early stage NSCLC from 2,200 cGy times three to 700 cGy times ten. Excellent local control and survival have been observed for older patients whose medical conditions precluded surgery (76). In a randomized study of neoadjuvant immunotherapy for early stage NSCLC, the combination of CPI and SBRT was well tolerated and lead to a significant pathologic response compared to immunotherapy alone (77). Among patients with locally advanced NSCLC, the common fractionation ranges from a total dose of 4,500 to 8,550 cGy in 230 to 350 cGy per fraction (78). Good local control with acceptable toxicity were observed when hypofractionated radiotherapy was combined with chemotherapy (78). A meta-analysis of patients with locally advanced NSLCC also corroborated the safety of hypofractionated radiotherapy in combination with chemotherapy (79). Grade 3–4 esophagitis and pneumonitis remained the limiting factor for dose escalation with hypofractionated radiotherapy (80). However, preliminary results from hypofractionated IGRT for locally advanced NSCLC reported a higher survival and progression-free survival compared to the conventional radiotherapy technique with comparable toxicity most likely due to the higher biologic equivalent dose (BED) (81). Median survival, local control, and grade 3–4 toxicity were 42 months, 43%, 42.1% and 32 months, 31%, and 47.6% for the hypofractionated group and conventional fractionated group, respectively. Except for one study, other studies also corroborated the safety and efficacy of hypofractionated IGRT for locally advanced NSCLC (42,82,83). The lone study which demonstrated increased toxicity leading to a poor survival despite a better local control used a higher fraction dose of 400 cGy (82). Thus, it seems prudent to limit the daily fraction dose from 250 to 300 cGy in future hypofractionated IGRT studies for NSCLC because of the large radiotherapy field required to cover both the tumor and mediastinal lymph nodes. Another option to reduce toxicity is to deliver a higher dose to the primary tumor and a reduced dose to the mediastinal node (84) or to treat the primary tumor with SBRT (85). Thus, there are many options for dose escalation with hypofractionated IGRT. *Table 2* summarizes studies using hypofractionated IGRT for locally advanced NSCLC.

The combination of hypofractionated IGRT and RDCPI may improve local control, reduce treatment toxicity, and cost effective for this vulnerable population with locally advanced NSCLC. Selection is the key as patients with high TPS expression are most likely to benefit from this combined treatment. Biomarkers should be performed prior to treatment to select patients who are more likely to respond to targeted agents because the favorable toxicity profile of those agents.

As an international research group with a large network of over 1,100 cancer institutions in 127 countries, the International Geriatric Radiotherapy Group (IGRG) can propose specific protocols combining RDCPI administration in combination with hypofractionated IGRT for older NSCLC with locally advanced disease and high expression (86-88). Toxicity, survival, and QOL can be assessed and promoted to encourage participation of older NSCLC patients in clinical trials.

Conclusions

Immunotherapy with RDCPI combined with hypofractionated IGRT may be an attractive concept to recruit selected older patients with locally advanced NSCLC and HPD-L1 expression in clinical protocols. We postulate that toxicity and patient QOL may be improved with this innovative treatment. Clinical studies should be

Table 2 Summary of studies using hypofractionated image-guided radiotherapy for locally advanced non-small cell lung cancer

Study	Patient No.	Chemo	Dose	Survival	Local control	Toxicity	Follow-up (months)
Zhang *et al.* (81)	86	Yes	Total: 6,000 cGy	Median: 42 months	43%	42.10% gr. 3+4	23
			Fraction: 300 cGy				
	73		Total: 6,250 cGy				
			Fraction: 250 cGy				
	57		Total: 6,000 cGy	Median: 32 months	31%	47.60% gr. 3+4	
			Fraction: 200 cGy				
Agolli *et al.* (42)	60	No	Total: 6,000 cGy	2-year: 40%	2-year: 53%	17% gr. 3	NS
			Fraction: 300 cGy				
Iyengar *et al.* (82)	50	No	Total: 6,000 cGy	1-year: 37.7%	2-year: 85.8%	30% gr. 3; 2% gr. 4; 4% gr. 5	NS
			Fraction: 400 cGy				
	46		Total: 6,000 cGy	1-year: 44.6%	2-year: 66.1%	30% gr. 3; 2% gr. 4; 6% gr. 5	
			Fraction: 200 cGy				
Adkison *et al.* (83)	46 (80% Stage III)	Yes	Dose escalation	2-year: 46%	69.60%	0 gr. 3+4	8
			Total: 5,700 to 8,050 cGy				
			Fraction: 228 to 322 cGy				

Chemo, chemotherapy; cGy, centigray; gr., grade; NS, not specified.

performed to test this hypothesis.

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Footnote

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

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