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Special Article

Palliative thoracic radiation therapy for non-small cell lung cancer: 2018 Update of an American Society for Radiation Oncology (ASTRO) Evidence-Based Guideline

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Abstract

Purpose: To revise the recommendation on the use of concurrent chemotherapy (CC) with palliative thoracic external beam radiation therapy (EBRT) made in the original 2011 American Society for Radiation Oncology guideline on palliative thoracic radiation for lung cancer.

Methods and materials: Based on a systematic PubMed search showing new evidence for this key question, the task force felt an update was merited. Guideline recommendations were created using

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Conflicts of interest. Before initiating work on this guideline update, task force members completed disclosure statements, and pertinent disclosures are published within this report. These disclosures were reviewed by the task force chair and determined there are no relationships that present a conflict with respect to these task force members' work on this guideline update. George Rodrigues: President of and stock in George Rodrigues Medicine Professional Corporation, royalties from Demos Medical Publishing. American Society for Radiation Oncology (ASTRO) guidelines present scientific, health, and safety information and may reflect scientific or medical opinion. They are available to ASTRO members and the public for educational and informational purposes only. Commercial use of any content in this guideline without the prior written consent of ASTRO is strictly prohibited. Adherence to this guideline will not ensure successful treatment in every situation. This guideline should not be deemed inclusive of all proper methods of care or exclusive of other methods reasonably directed to obtaining the same results. The physician must make the ultimate judgment regarding any specific therapy in light of all circumstances presented by the patient. ASTRO assumes no liability for the information, conclusions, and findings contained in its guidelines. This guideline cannot be assumed to apply to the use of these interventions performed in the context of clinical trials. This guideline was prepared based on information available at the time the panel was conducting its research and discussions on this topic. There may be new developments that are not reflected in this guideline and that may, over time, be a basis for ASTRO to revisit and update the guideline.

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a predefined consensus-building methodology supported by American Society for Radiation Oncology–approved tools for grading evidence quality and recommendation strength.
Results: Although few randomized clinical trials address the question of CC combined with palliative thoracic EBRT for non-small cell lung cancer (NSCLC), a strong consensus was reached among the task force on recommendations for incurable stage III and IV NSCLC. For patients with stage III NSCLC deemed unsuitable for curative therapy but who are (1) candidates for chemotherapy, (2) have an Eastern Cooperative Oncology Group PS of 0 to 2, and (3) have a life expectancy of at least 3 months, administration of a platinum-containing chemotherapy doublet concurrently with moderately hypofractionated palliative thoracic radiation therapy is recommended over treatment with either modality alone. For patients with stage IV NSCLC, routine use of concurrent thoracic chemoradiation is not recommended.
Conclusions: Optimal palliation of patients with incurable NSCLC requires coordinated interdisciplinary care. Recent data establish a rationale for CC with palliative thoracic EBRT for a well-defined subset of patients with incurable stage III NSCLC. For all other patients with incurable NSCLC, data remain insufficient to support this treatment approach.

Introduction

Lung cancer (LC) remains the leading cause of cancer mortality in the United States, and non-small cell LC (NSCLC) represents nearly 90% of all lung cancer diagnoses.[1] More than one-half of patients with NSCLC are diagnosed with locally advanced (stage III) and advanced (stage IV) disease.[2] Because palliative thoracic radiation therapy plays an important role for these patients, the American Society for Radiation Oncology (ASTRO) published a clinical practice guideline on this topic in 2011.[3] The guideline addressed 3 key questions (KQs) related to palliative thoracic external beam radiation therapy (EBRT): (1) dose and fractionation for EBRT, (2) utility of endobronchial brachytherapy, and (3) appropriateness of concurrent chemotherapy (CC) in combination with EBRT.

In light of recent level 1 evidence supporting use of CC in combination with palliative thoracic EBRT for patients with NSCLC, this update aims to revise the recommendation for KQ3. The new recommendations for KQ3 and those for KQ1 and KQ2 from the 2011 ASTRO guideline, which were not changed in this update, are shown in eTable 1 (available as supplementary material online only at www.practicalradonc.org). In keeping with the original guideline, the scope of this update does not cover the clinical decision regarding whether to treat a patient with palliative or curative intent but, rather, addresses the narrower question of optimal treatment with thoracic radiation and chemotherapy in patients for whom the decision has been made to treat palliatively. Whether there is a subset of patients with oligometastatic NSCLC who benefit from intensified treatment delivered with a more aggressive intent is beyond the scope of the original guideline and this update. This guideline is endorsed by the European Society for Radiotherapy & Oncology and the Royal Australian and New Zealand College of Radiologists.

Methods and materials

Process

In February 2016, this 2011 guideline was considered for an update in accordance with current ASTRO policy. The guidelines subcommittee convened a work group composed of 1 colead from the original guideline (G.R.), 2 outside topic experts not involved in the original guideline (A.C. and M.K.), and 2 guidelines subcommittee members (B.M. and S.Z.). An updated literature search yielded no new prospective data relevant to KQ1 or 2 and, therefore, these statements were left as originally written. New randomized clinical trials (RCTs), however, were found addressing KQ3; therefore, the work group recommended a guideline update focused on use of CC combined with palliative thoracic EBRT for patients with NSCLC. The proposal was approved by the ASTRO Board of Directors in July 2016. The task force was made up of the work group members with the addition of a radiation oncology resident (E.H.B.), a community practice representative (K.M.C.), and a medical oncologist (G.G.).

Through calls and e-mails, the task force formulated recommendation statements and narrative based on the literature review. The draft guideline was reviewed by 3 expert reviewers (see Acknowledgments) and ASTRO legal counsel. The update was posted online for public comment in June and July 2017. The Board of Directors approved the final document in February 2018.

Literature review

A systematic review was conducted of English--language studies in PubMed published between the last date searched in the original guideline, March 1, 2010, and July 27, 2016. Both MeSH terms and text words were used. The outcomes of interest were overall survival (OS),

local and regional control, distant failure, toxicity, and quality of life (QOL). In total, 113 references were retrieved and reviewed. The inclusion criteria were: age ≥18 years and patients with locally advanced or metastatic lung cancer treated with radiation therapy with palliative intent. The exclusion criteria were: curative intent, pediatric studies, non-human, dosimetric-only, case report, and conference abstract. Ultimately, 31 RCTs, meta-analyses, and prospective studies were included and abstracted into evidence tables.

Grading of evidence, recommendations, and consensus methodology

When available, high-quality data formed the basis of the statements in accordance with the National Academies of Science, Engineering, and Medicine's Health and Medicine Division (formerly Institute of Medicine) standards[4] and a modified Grading of Recommendations, Assessment, Development, and Evaluations methodology was used.[5,6] Recommendations were classified as "strong" or "conditional." A strong recommendation indicated the task force was confident the benefits of the intervention clearly outweighed the harms, or vice versa, and "all or almost all informed people would make the recommended choice for or against an intervention."[6] A conditional recommendation shows the balance between risks and benefits is even or uncertain and there is a larger role for individual preferences and shared decision making.

The quality of evidence underlying each recommendation statement was categorized as high, moderate, or low. These quality levels indicated:

- "High: We are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
- Low: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect."[5]

Consensus was evaluated through a modified Delphi approach adapted from the American Society of Clinical Oncology process.[7] Task force members completed an online survey to rate their agreement with each recommendation on a 5-point Likert scale, ranging from strongly disagree to strongly agree. A prespecified threshold of ≥75% of raters selecting "agree" or "strongly agree" indicated consensus was achieved. If a recommendation statement did not meet this threshold, it was modified and resurveyed.

Results

KQ: What is the role of chemotherapy administered concurrently with radiation for the palliation of LC?

Incurable stage III NSCLC

Statement A: In the management of patients with stage III NSCLC deemed unsuitable for curative therapy but who are (1) candidates for chemotherapy, (2) have an Eastern Cooperative Oncology Group (ECOG) PS of 0 to 2, and (3) have a life expectancy of at least 3 months, administration of a platinum-containing chemotherapy doublet concurrently with moderately hypofractionated palliative thoracic radiation therapy is recommended over treatment with either modality alone.

Recommendation strength: Strong
Quality of evidence: Moderate
Consensus: 100%

Narrative

There are 3 RCTs (eTable 2; available as supplementary material online only at www.practicalradonc.org) addressing the question of CC and thoracic EBRT for patients with incurable NSCLC. The study by Ball et al was the only 1 published at the time the original ASTRO palliative lung guideline was written. This was a phase III trial enrolling 200 patients with 1:1 randomization between radiation alone (2000 cGy in 5 fractions) and the same radiation dose given concurrently with a single week of infusional 5-fluorouracil (1 g/m^2/day). CC significantly improved overall response rates, from 16% to 39%, but not OS, progression-free survival, symptom burden, or QOL. Acute esophagitis was significantly worse with CC (eTable 3).[8] These findings led the original ASTRO palliative lung guideline authors to recommend against CC; however, there are 2 important limitations of this study. First, eligibility criteria were not well defined. Eligible patients were to be incurable, but parameters for curability were not laid out, and American Joint Committee on Cancer stage was not specified. Perhaps more important a limitation was the use of 5-fluorouracil alone as the CC agent; modern evidence overwhelmingly supports platinum-containing chemotherapy as being most active against NSCLC.[9]

The 2 other RCTs were reported after publication of the original guideline. These trials draw different conclusions than Ball et al. The first, Nawrocki et al, was a phase II RCT enrolling 99 patients with protocol-specified incurable stage III NSCLC in a 1:1 randomization between radiation alone (3000 cGy in 10 fractions) versus the same radiation dose delivered concurrent with the third of 3 cycles of cisplatin/vinorelbine (cisplatin 80 mg/m^2 on day 1, vinorelbine 25 mg/m^2 on days 1 and 8).[10] Eligibility criteria included an ECOG performance status (PS) of 0 to 2.

Patients were defined as incurable based on an forced expiratory volume in 1 second ≤40% of predicted or a gross tumor volume >8 cm in maximum diameter. CC significantly improved median survival (9 to 12.9 months), 1-year OS (25% to 57%), and 2-year OS (6% to 24%). CC significantly worsened grade 3 to 4 neutropenia (22% vs 0%), but no other differences in high-grade toxicity were seen, including esophagitis (eTable 3). CC did not improve pain control or pulmonary symptom relief during follow-up. Formal QOL studies were not performed.

The second study, Strom et al, was a phase III RCT enrolling patients with protocol-specified incurable stage III NSCLC in a 1:1 randomization between 4 cycles of chemotherapy alone (carboplatin area under the curve = 5 on day 1, vinorelbine 60 mg/m^2 on days 1 and 8) versus EBRT (4200 cGy in 15 fractions) given concurrently with cycle 2 of the same chemotherapy regimen.[11] The trial was designed to accrue 350 patients over 3 years, but was terminated early after accruing 191 patients in 5 years. Incurability was defined as gross tumor volume ≥8 cm in maximum diameter or 10% weight loss in 6 months. An ECOG PS ≥2 was an inclusion criterion for incurability, but nearly 80% of the patients enrolled had an ECOG PS of 0 to 1, and none had an ECOG PS ≥3. CC significantly improved median survival (9.7 to 12.6 months), 1-year OS (34% to 53%), and 2-year OS (7% to 28%). Grade 5 toxicity was uncommon, and rates were similar between arms. CC significantly increased grade 3 esophagitis rates (30% vs 1.5%), but no grade 4 reactions were reported; however, at a later follow-up point, QOL, social functioning, and physical functioning scores were better preserved in the CC group.[11] The greatest QOL advantage with chemoradiation was for patients with the bulkiest disease (tumor volumes >7 cm).[12] In another subset analysis, the advantages of CC appeared preserved for the elderly.[13]

Both of these recent studies have limitations. Perhaps the largest is the undefined nature of this patient population. To our knowledge, there are no validated criteria to define which stage III NSCLC patients are eligible for curative treatment. Nevertheless, studies indicate many stage III NSCLC patients are treated with palliative intent in clinical practice. One recent Canadian study found that approximately one-half of this population is not treated curatively, with weight loss and performance status heavily affecting treatment intent.[14,15] It is beyond the scope of this guideline update to define curability for stage III NSCLC, but knowing that these patients are frequently treated with palliative intent, we view RCT data on how this treatment should be delivered as valuable. Ultimately, we leave it to the discretion of the prescribing physicians to determine parameters for curability, acknowledging that poor PS, weight loss, and inability to achieve dosimetric goals likely provide the best guidance. The extent to which these patients are routinely treated with curative intent in one's practice, however, will obviously impact the applicability of this guideline update.

Other limitations are also worth noting. There was variability in the amount of postprotocol therapy delivered. Although this limitation is common to studies of palliative care, its impact here may be significant. For the study by Nawrocki et al, for example, only about 1 in 4 patients on the EBRT alone arm received chemotherapy after completion of protocol therapy.[11] Given that 100% of patients on the combined modality arm received at least some chemotherapy, it is perhaps not surprising the authors found differences in survival and QOL between the groups. Also, some patients were not able to complete per-protocol therapy. Nawrocki et al reported only 69% of patients completed all 3 cycles of chemotherapy on the combined modality arm. Because radiation was given concurrently with cycle 3 of chemotherapy, this presumably means more than one-third of patients received sequential rather than concurrent chemoradiation.[10] Finally, neither study incorporated positron emission tomography/computed tomography or brain magnetic resonance imaging in the protocol-specified diagnostic workup; therefore, the possibility of stage migration should be considered when extrapolating these results to a setting where these tests are routine.

All 3 RCTs show increased acute morbidity associated with CC, principally related to esophagitis (eTable 3). Two of the 3 trials report significantly increased rates of esophagitis with CC, though the rates of high-grade esophagitis vary widely, from 2% to 30%. The study with the highest rate of grade 3 esophagitis also reports a 2-fold higher rate of hospitalization associated with CC.[11]

Toxicity concerns merit careful attention when patients are being treated with palliative intent; however, the QOL data from the Strom study place these toxicity findings in an important context, suggesting there is a temporary tradeoff in QOL during chemoradiation that is offset by gains in global QOL scores over time, presumably related to improved durability of symptom palliation from more aggressive therapy. These gains will be larger for those with longer survival times, underscoring the importance of not extrapolating these findings beyond those patients matching key eligibility criteria in these studies.

Along those lines, these criteria are underscored in recommendation Statement A to emphasize the clinical scenarios where the data best apply. Three of the 5 parameters in Statement A are taken directly from eligibility criteria of the reviewed literature (stage III NSCLC, suitable for chemotherapy, but unsuitable for curative chemoradiation). Given that "unsuitability for curative therapy" was either left undefined or was poorly overlapping on the studies reviewed, this is not further specified here. The other 2 parameters in Statement A (ECOG PS 0 to 2, life expectancy at least 3 months) are based on the facts that all patients on the Nawrocki and Strom studies had an ECOG PS between 0 and 2, and that

the Strom et al data show the QOL advantages to CC are realized no sooner than 3 months after completion of treatment.[11] Given the relatively narrow therapeutic window, these parameters should be followed closely.

There is some guidance in the RCTs cited here on how to deliver CC in this setting. Both the Nawrocki and Strom trials used platinum/vinorelbine doublets with thoracic EBRT, suggesting this regimen is tolerable. Others have studied palliative thoracic EBRT given concurrently with cisplatin and either docetaxel, paclitaxel, or pemetrexed, with acceptable esophagitis rates (0% grade 4, 6.6% grade 3).[16] Based on these data, we opted to endorse platinum-containing doublets in recommendation Statement A.

In regards to EBRT, the Nawrocki and Strom trials called for daily doses of 280 or 300 cGy per fraction, to cumulative doses of 3000 or 4200 cGy. We opted to refer to those doses in the recommendation statement as "moderate hypofractionation."[10,11] There are 2 reasons to emphasize this dose range. First, the evidence CC is limited to patients treated to an EBRT dose of at least 3000 cGy and, therefore, there are uncertainties about its value for patients treated with lower EBRT doses. There are ample data for lower doses when palliative thoracic EBRT is used on its own (as summarized in the original ASTRO guideline on this subject), but these doses cannot be recommended when thoracic EBRT is given with CC because of a lack of supporting evidence. The appropriate indications for relatively more hypofractionated EBRT alone versus relatively less hypofractionated EBRT with CC merit further study. The second important issue related to the EBRT fraction size is its anticipated relationship with acute esophagitis. Studies investigating hypofractionated thoracic EBRT with CC in the curative setting have demonstrated an association between grade 3 radiation esophagitis and the radiation dose per fraction delivered to the esophagus[17]; however, these studies typically use much higher cumulative doses of radiation than would be typical in the palliative setting and, therefore, it is unclear how relevant these findings are to the current question. There is no clear trend between grade 3 esophagitis and EBRT fraction size or cumulative delivered EBRT doses in the 3 trials reviewed here. Moreover, there is insufficient information provided on radiation technique in any of the 3 studies to comment on methods used to prevent esophagitis. Nevertheless, given we have no data for daily doses >300 cGy per fraction or cumulative doses >4200 cGy when given with CC, we suggest avoiding higher doses to minimize risks of grade 3 radiation esophagitis and hospitalization. Certainly, best practice also includes minimizing unnecessary radiation dose to the esophagus when palliative thoracic EBRT is given with CC.

Stage IV NSCLC

Statement B: In the palliative management of patients with stage IV NSCLC, routine use of concurrent thoracic chemoradiation is not recommended. This practice should remain primarily reserved for clinical trials or multi-institutional registries.

Recommendation strength: Strong
Quality of evidence: Low
Consensus: 100%

Narrative

There is currently no level 1 evidence to support use of CC with palliative thoracic EBRT for patients with stage IV NSCLC. There are nonrandomized prospective data on this question reporting favorable survival versus historical controls, but their nonrandomized nature confounds their interpretation.[16,18,19] Moreover, recent database analyses suggest no apparent survival benefit associated with this practice.[20] Nevertheless, unfortunately, nearly 1 in 5 stage IV NSCLC patients receive CC with thoracic EBRT, with practice setting and insurance status predicting practice patterns.[21] Again, because patients with stage IV NSCLC face median survival times approximately one-half of those seen for incurable stage III NSCLC on the studies summarized previously, the QOL improvements attributed to CC for stage III NSCLC may not be realized by most patients with stage IV NSCLC because the decrement in QOL caused by aggressive treatment takes months to resolve. As such, we feel the current available data do not support the routine use of CC with palliative thoracic EBRT for patients with stage IV NSCLC, and we graded this recommendation as "strong," in spite of the low quality of evidence, based on the significant risks of patient harm associated with CC in this setting.

Conclusion

Optimal palliation for patients with incurable NSCLC requires coordinated interdisciplinary care. Recent data establish a rationale for CC with palliative thoracic EBRT for a well-defined subset: those with incurable stage III NSCLC who are candidates for chemotherapy. For all other patients with incurable NSCLC, data remain insufficient to support CC with palliative thoracic EBRT.

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