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Guideline Observation

Updates of the NCCN guidelines for small cell lung cancer

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Updates in Version 2.2018 of the NCCN guidelines for small cell lung cancer from version 1.2018

The Discussion section has been updated to reflect the changes in the algorithm. (MS-1)

Updates in version 1.2018 of the NCCN guidelines for small cell lung cancer from version 3.2017

For consistency in imaging, statement was revised: "CT Chest / liver / adrenal" was replaced by "Chest / abdomen CT" with contrast.

Initial evaluation

Delete "Ca LDH", add "BUN"; Add "(skull base to mid-thigh)" to PET/CT scan, (if limited stage is suspected).

Footnote "b" for H & P was added: "See Signs and Symptoms of Small Cell Lung Cancer (SCL-A)" (Also for SCL-5).

Footnote "c" for pathology review was added: "See Principles of Pathologic Review (SCL-B)".

Additional workup

"During evaluation for surgery" was added to Pulmonary function tests (PFTs)

"(Consider biopsy if bone imaging is equivocal)" was added.

Adjuvant treatment

Clinical stage N+ separated into N1 and N2.

N1 adjuvant treatment option added: "Systemic therapy ± mediastinal RT (sequential or concurrent)"

N2 adjuvant treatment option added: "Systemic therapy + mediastinal RT (sequential or concurrent)".

Footnote "o"

Footnote "o" was modified: "For patients receiving adjuvant therapy, response assessment should occur only after completion of adjuvant therapy (SCL-5); do not repeat scans to assess response during adjuvant treatment."

Initial treatment of asymptomatic brain metastases

Statement was modified: "May administer the whole-brain RT after completion of systemic therapy".

Updates in version 1.2018 of the NCCN guidelines for small cell lung cancer from version 3.2017

Response assessment following initial therapy

Bullet 5 was modified: "Electrolytes, LFTs, BUN, creatinine". Deleted "Ca".

Adjuvant treatment; extensive disease

"PCI ± thoracic RT" revised to "Consider PCI ± thoracic RT".

Surveillance

Footnote "s" was added to heading: "See NCCN Guidelines for Survivorship".

Complete response or partial response

Limited stage

Statement was revised: "After completion of initial therapy" instaed of "After recovery from primary therapy".

Bullet 1 was revised: "Oncology follow-up visits every 3–4 mo during y 1–2, every 6 mo during y 3–5, then

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annually".

Bullet 1 revised: "At every visit: H&P, CT Chest/ abdomen with contrast (delete liver/adrenal), bloodwork only as clinically indicated".

Bullet 2 was added: "If PCI not given, then MRI (preferred) or CT brain with contrast every 3–4 mo during y 1–2".

Extensive stage

Statement was added: "After completion of initial or subsequent therapy".

Bullet 1 was added: "Oncology follow-up visits every 2 mo during y 1, every 3–4 mo during y 2-3, then every 6 mo during years 4–5, then annually".

Bullet 1 revised: "At every visit: H&P, CT Chest/ abdomen with contrast (delete liver/adrenal), bloodwork only as clinically indicated".

Bullet 2 was added: "If PCI not given, then MRI (preferred) or CT brain with contrast every 3–4 mo during y 1–2".

Footnote "u" for thoracic RT was revised: "Sequential radiotherapy to thorax in selected patients, especially with residual thoracic disease and low-bulk extrathoracic metastatic disease that has responded to systemic therapy." Deleted "complete response".

Stable disease

Limited stage and Extensive stage

Statement was revised: "After completion of initial therapy" delete "recovery from primary therapy".

Bullet 1 was revised: "Oncology follow-up visits every 3–4 mo during y 1–2, every 6 mo during y 3–5, then annually".

Statement was added: "After completion of initial or subsequent therapy".

Bullet 1 was added: "Oncology follow-up visits every 2 mo during y 1, every 3–4 mo during y 2–3, then every 6 mo during years 4–5, then annually".

SCL-6

Footnote "k," "See Principles of Supportive Care (SCL-D)" was added after all "Palliative symptom management" statements.

Footnote "v," "See Principles of Palliative Care (PAL-1)" was added after all "Palliative symptom management" statements.

For "PS 0-2," "or" was removed from between "Consider subsequent systemic therapy" and "Palliative symptom management, including localized RT to symptomatic sites".

(SCL-A) signs and symptoms of small cell lung cancer

A new section was added: "Signs and Symptoms of Small Cell Lung Cancer".

(SCL-B) principles of pathologic review

A new section was added: "Principles of Pathologic Review".

(SCL-C) principles of surgical resection

A footnote was removed: "Slotman B, Faivre-Finn C, Kramer G, *et al*. Prophylactic cranial irradiation in extensive small-cell lung cancer. N Engl J Med 2007; 357: 664-672."

(SCL-D) principles of supportive care

Syndrome of inappropriate antidiuretic hormone

Sub-bullet 5 was revised: "Vasopressin receptor inhibitors (conivaptan, tolvaptan) for refractory hyponatremia".

(SCL-E) principles of systemic therapy (1 of 3)

Extensive stage (maximum of 4–6 cycles)

Bullet 7 was revised: "Cisplatin 30 mg/m2 days 1, 8 and irinotecan 65 mg/m2 days 1, 8".

Footnote "†" was added: "If not used as original regimen, may be used as therapy for primary progressive disease."

Subsequent systemic therapy

Footnote "‡" was added: "Subsequent systemic therapy refers to second-line and beyond therapy."

Relapse ≤ 6 mo, PS 0-2: nivolumab ± ipilimumab

Reference "22" was added: "Hellmann MD, Ott PA, Zugazagoitia J, et al. First report of a randomized expansion cohort from CheckMate 032 [abstract]. J Clin Oncol 2017;35: Abstract 8503."

(SCL-E) principles of systemic therapy (2 of 3)

Limited-stage

Sub-bullet 1 was revised: "For patients receiving adjuvant therapy, response assessment should occur only after completion of adjuvant therapy; do not repeat scans to assess response during adjuvant treatment."

(SCL-F) principles of radiation therapy (1 of 3)

General Principles

Bullet 4 was revised: "Use of more advanced technologies is appropriate when needed to deliver adequate tumor doses while respecting normal tissue dose constraints. Such technologies include (but are not limited to) 4D-CT and/or PET/CT simulation, IMRT/ VMAT, IGRT, and motion management strategies. IMRT is preferred over 3D conformal external-beam RT (CRT) on the basis of reduced toxicity in the setting of concurrent chemotherapy/RT. Quality assurance measures are essential and are covered in the NSCLC guidelines (see NSCL-C)."

Reference "1" was added: "Chun SG, Hu C, Choy H, *et al*. Impact of intensity-modulated radiation therapy

technique for locally advanced non-small-cell lung cancer: a secondary analysis of the NRG oncology RTOG 0617 randomized clinical trial. J Clin Oncol 2017; 35: 56–62."

Limited Stage

Bullet 5 was revised: "Dose and schedule: For limited-stage SCLC, the optimal dose and schedule of RT have not been established; 45 Gy in 3 weeks (1.5 Gy twice daily [BID]) is superior (category 1) to 45 Gy in 5 weeks (1.8 Gy daily). When BID fractionation is used, there should be at least a 6-hour inter-fraction interval to allow for repair of normal tissue. If using once-daily RT, higher doses of 60–70 Gy should be used. The current randomized trial CALGB 30610/RTOG 0538 is comparing the standard arm of 45 Gy (BID) in 3 weeks to 70 Gy in 7 weeks; accrual to an experimental concomitant boost arm has closed. The European CONVERT trial demonstrated comparable overall survival and toxicity between 45 Gy (BID) and 66 Gy (daily)."

Reference 20 was added: "Faivre-Finn C, Snee M, Ashcroft L, *et al* Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): an open-label, phase 3, randomised, superiority trial. Lancet Oncol 2017; 18: 1116-1125."

Extensive stage

Bullet 1 modified: "Consolidative thoracic RT is beneficial for selected patients with extensive-stage SCLC with CR or good response to systemic therapy. Studies have demonstrated that consolidative thoracic RT up to definitive doses is well tolerated, results in fewer symptomatic chest recurrences, and improves long-term survival in some patients. The Dutch CREST randomized trial of modest-dose thoracic RT (30 Gy in 10 fractions), in patients with extensive stage SCLC that responded to systemic therapy demonstrated significantly improved 2-year overall survival and six-month PFS, although the protocol-defined primary endpoint of one-year overall survival was not significantly improved. Subsequent exploratory analysis found the benefit of consolidative thoracic RT is limited to the majority of patients who had residual thoracic disease after systemic therapy."

Bullet 2 was added: "Dosing and fractionation of consolidative thoracic RT should be individualized within the range of 30 Gy in 10 daily fractions to 60 Gy in 30 daily fractions, or equivalent regimens in this range."

Reference 24 was added: "Slotman BJ, van Tinteren H, Praag JO, *et al*. Radiotherapy for extensive stage small-cell lung cancer– Authors reply. Lancet 2015; 385: 1292–1293."

Prophylactic Cranial Irradiation (PCI)

Bullet 1 modified: "In patients with limited-stage SCLC who have a good response to initial therapy, PCI decreases brain metastases and increases overall survival (category 1).

In patients with extensive-stage SCLC that has responded to systemic therapy, PCI decreases brain metastases. A randomized trial conducted by the EORTC found improved overall survival with PCI. However, a Japanese randomized trial found that in patients who had no brain metastases on baseline MRI, PCI did not improve overall survival compared with routine surveillance MRI and treatment of asymptomatic brain metastases upon detection. In patients not receiving PCI, surveillance for metastases by brain imaging should be considered performed."

Bullet 5 was added: "When administering PCI, consider adding memantine during and after RT, which has been shown to decrease neurocognitive impairment following whole brain radiation therapy (WBRT) for brain metastases."

Reference 28 was updated: "Takahashi T, Yamanaka T,Takashi S et al. Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 2017; 18: 663–671."

Reference 31 was added: "Brown PD, Pugh S, Laack NN, *et al*. Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. Neuro Oncol 2013; 10: 1429–1437."

Brain Metastases

Bullet 1 modified: "Brain metastases should be treated with WBRT rather than stereotactic radiotherapy/ radiosurgery (SRT/SRS) alone, because these patients tend to develop multiple CNS metastases. In patients who develop brain metastases after PCI, repeat WBRT may be considered in carefully selected patients. SRS, is preferred if feasible, especially if there has been a long-time interval from initial diagnosis to occurrence of brain metastases and there is no uncontrolled extracranial disease."