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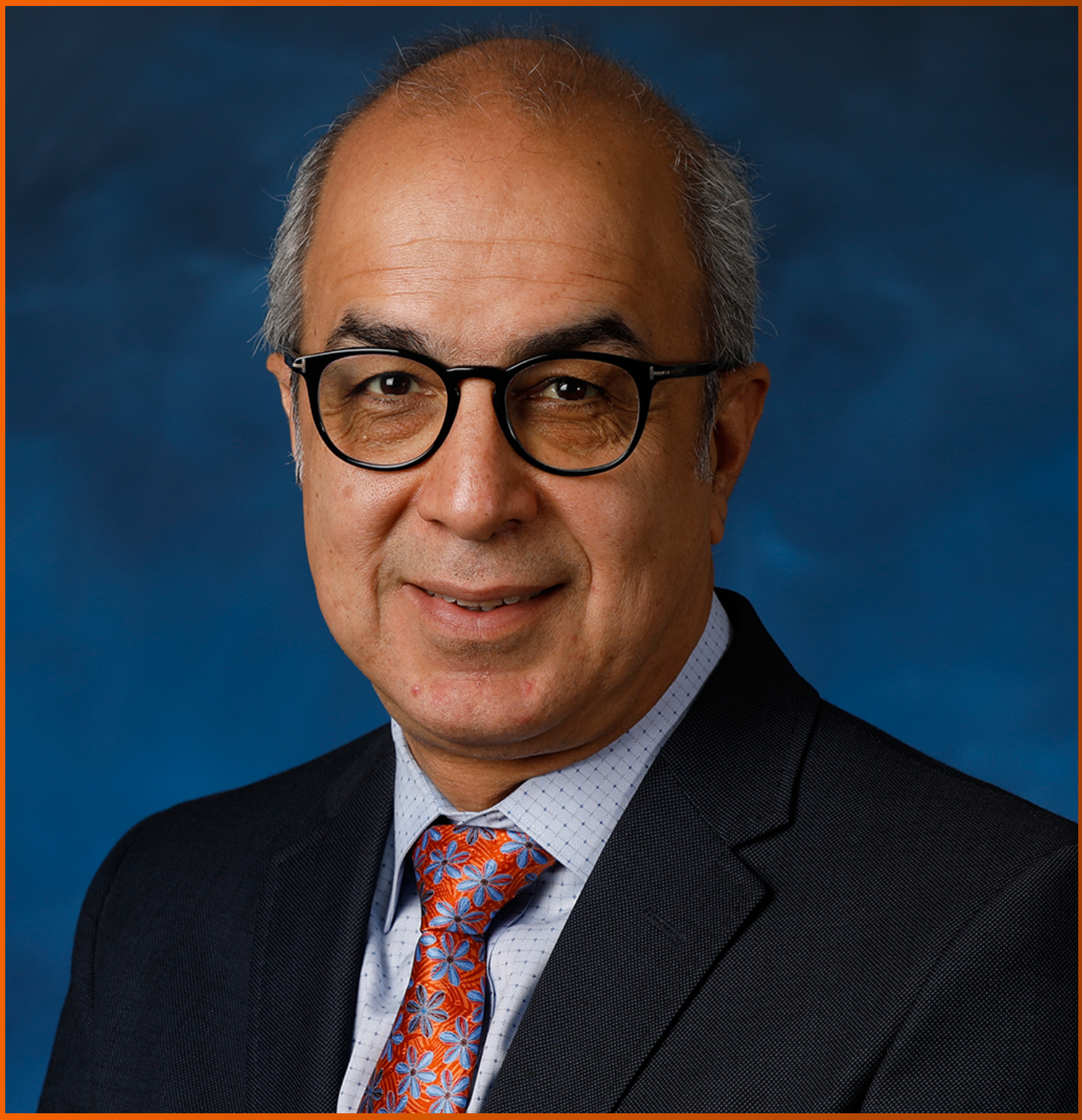

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MINIREVIEWS

Adjuvant therapy for lung neuroendocrine neoplasms

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Abstract

Pulmonary neuroendocrine neoplasms (NENs) represent a minority of lung cancers and vary from slower growing pulmonary carcinoid (PC) tumors to aggressive small cell lung cancer (SCLC). While SCLC can account for up to 15% of lung cancer, PCs are uncommon and represent about 2% of lung cancers. Surgical resection is the standard of care for early-stage PCs and should also be considered in early stage large cell neuroendocrine carcinoma (LCNEC) and SCLC. Adjuvant treatment is generally accepted for aggressive LCNEC and SCLC, however, less well established for PCs. Guidelines admit a lack of trials to support a high-level recommendation for adjuvant therapy. This manuscript will discuss the role for adjuvant therapy in NENs and review the available literature.

Key Words: Neuroendocrine; Adjuvant therapy; Lung; Pulmonary carcinoid; Small cell lung cancer

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Core Tip: Neuroendocrine neoplasms of the lung are uncommon malignancies. They vary in degrees of aggressiveness from the slow growing typical carcinoid tumors to the very fast-growing small cell lung cancer. While surgical resection should be considered for early-stage disease, the role of adjuvant therapy is less well established. Guidelines from different organizations vary, citing a lack of trials to support a high-level recommendation. This manuscript will discuss the evidence for and against adjuvant therapy in neuroendocrine neoplasms of the lung.

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INTRODUCTION

Neuroendocrine neoplasms (NENs) are heterogenous tumors derived from neuroendocrine cells, which are located throughout the body, including organs such as the thyroid, pancreas, genitourinary tract, gastrointestinal tract, and the lungs[1]. Most are found in the abdomen as gastrointestinal neuroendocrine tumors (50%-60%), but approximately 20%-30% are found in the lung[2]. Lung NENs are derived from the foregut and are thought to arise from specialized bronchopulmonary cells called Kulchitsky cells[1]. There are no known risk factors for low grade tumors; however, smoking is the major risk factor for high grade NENs[3].

Clinically, lung NENs behave very differently depending on grade and stage. The 2015 World Health Organization Classification assigns lung NENs into four categories: typical carcinoid (TC) low grade, atypical carcinoid (AC) intermediate grade, large cell neuroendocrine carcinoma (LCNEC), and small cell lung cancer (SCLC)[4]. These categories are based on mitotic rate, presence of necrosis, and cytological details. Specifically, TCs are defined as mitotic rate < 2 mitoses per high powered field (HPF) without necrosis, whereas ACs have a mitotic rate from 2-10/HPF with or without necrosis. The mitotic rate for both LCNEC and SCLC is > 10/HPF with extensive necrosis. The current staging follows the American Joint Committee on Cancer 8th edition for lung cancer[5]. Each category has a markedly different biological behavior with different prognostic features and treatments, making accurate diagnosis imperative[6].

Lung NENs generally present similarly to other lung malignancies with symptoms such as dyspnea, cough, or hemoptysis but can also be found incidentally as an asymptomatic pulmonary nodule or mass[7]. Multiphasic contrast-enhanced computed tomography (CT) is the gold standard of diagnostic imaging[8]. Functional imaging with ^{68}Ga dotatate PET/CT or ^{64}Cu dotatate PET/CT is recommended for TCs and ACs after pathologic confirmation following a biopsy[9]. ^{18}F-FDG PET/CTs are generally most useful for higher grade tumors along with an MRI of the brain[8]. If patients are found to be metastatic, treatment options for TC/AC include somatostatin analogs[10], everolimus[11], combination chemotherapy with capecitabine/temozolomide[12], and radionuclide therapy[13]. Treatment for metastatic high grade tumors generally involves chemotherapy along with immunotherapy[14-16].

The treatment for early stage TC and AC is primarily surgical resection with active surveillance post operatively[8,17]. Surgical resection generally follows non-small cell lung cancer guidelines with lobectomy and mediastinal node sampling being the standard of care, however, there may be a role for sub-lobar resections in low grade tumors. Adjuvant chemotherapy is generally accepted for patients with high grade disease, however, the role for adjuvant treatment in TC and AC patients is less well established. This manuscript will discuss the use of adjuvant treatment in patients with lung NENs.

MAIN

Adjuvant treatment in typical and atypical carcinoid tumors

The mainstay of treatment for TC and AC tumors of the lung is surgical resection. Complete resection offers excellent progression-free survival rates of 97% and 80% in TC and AC patients, respectively[18]. The utility of adjuvant treatment is not as clear. There is limited data on the effectiveness of adjuvant therapy in the literature and treatment beyond surgery is controversial. The rarity of this tumor makes prospective, randomized control trial difficult (if not impossible) to conduct, leading to a paucity of data examining the role of adjuvant therapy in this uncommon malignancy.

Guidelines from the National Comprehensive Center Network (NCCN), European Neuroendocrine Tumor Society (ENETS), and the European Society of Medical Oncology (ESMO) both state that surgical resection alone is recommended for TC and AC patients with stage I or stage II disease and TC with stage III tumors, without the utilization of adjuvant therapy in this setting[8,19,20]. The recommendation for Stage III AC tumors differs slightly between these societies. ENETS calls for the consideration of adjuvant treatment in stage III AC patients who harbor positive lymph nodes[19], whereas NCCN states that one may consider cytotoxic chemotherapy with cisplatin and etoposide, carboplatin and etoposide, or temozolomide in stage III AC tumors regardless of lymph node status (NCCN 2021). However, the NCCN goes on to state there is limited data of the efficacy of chemotherapy. ESMO advises that adjuvant treatment consisting of chemotherapy with or without radiation therapy may be considered in patients who have an especially high risk of relapse, such as AC N2 patients after multidisciplinary consultation[20]. All groups call for an individualized, patient centered approach and shared decision making with each patient. In 2020, the North American Neuroendocrine Tumor Society and the Commonwealth Neuroendocrine Tumor Research Collaboration published an update and an endorsement of the 2015 ENETS guidelines indicating adjuvant therapy with somatostatin analogs, chemotherapy or radiation, is not recommended in lung neuroendocrine tumors after complete resection because of the lack of data[10]. Please see Table 1 for a summary of the current recommendations.

The absence of decisiveness in the guidelines is due to a lack of available data; however, there are multiple studies that do not support the use of adjuvant treatment in TC and AC tumors. Presently, there are five large, retrospective studies that fail to demonstrate the effectiveness of adjuvant therapy (consisting of radiation therapy or chemotherapy such as cisplatin and etoposide, carboplatin and etoposide, or temozolomide) in these low and intermediate grade bronchopulmonary tumors. Three studies examined adjuvant treatment in AC and TC patients with stage I, II, and III disease[21-23], one study assessed adjuvant therapy in TC node positive disease[24], and the last study analyzed adjuvant treatment in AC patients[25]. Please see the conclusions of these studies outlined in Table 2.

Westin *et al*[23] aimed to determine the impact of adjuvant chemotherapy in patients with AC and TC who had node positive disease without evidence of distant metastasis. Of the 8240 TC and 8259 AC patients identified *via* the National Cancer Database (NCDB), 6% and 40% of patients received adjuvant treatment, respectively. Adjuvant treatment was associated with significantly worse outcomes in TC patients (HR: 3.8; P = 0.004) and no OS benefit in patients with AC (HR: 1.1; P = 0.6). The authors concluded that adjuvant treatment may be harmful in those with TC[23].

Similarly, Wegner *et al*[21] utilized the NCDB to identify 662 patients with stage I, II, or III TC or AC who had undergone surgical resection followed by adjuvant treatment consisting of radiation therapy, chemotherapy, or chemoradiation. In this study, adjuvant treatment was not associated with a survival benefit in any stage, with median overall survival (mOS) being 114 mo for adjuvant therapy *vs* 117 mo for observation (P = 0.30). Specifically, for stage III disease, mOS favored observation (79 mo *vs* 63 mo; P = 0.89) Thus, the study concluded that adjuvant treatment should not be routinely used in this population[21].

Additionally, Gosain *et al*[22] conducted a retrospective study using the NCDB to examine the use of adjuvant chemotherapy in TC and AC tumors. This group identified 6673 patients (88% TCs and 12% AC). There was no survival benefit in those with TC who received adjuvant chemotherapy at any stage and patients did well with surgery alone. Adjuvant treatment in stage I AC patients was shown to be harmful, with patients having a 5-year OS of 84% for observation *vs* 52% chemotherapy (P < 0.01). Stage II AC showed a trend towards worse outcomes with adjuvant therapy with 5-year survival of 81% for observation *vs* 55% for adjuvant therapy (P = 0.34), however, without statistical significance potentially owing to the few patients available for analysis. Stage III AC patients trended towards a benefit from adjuvant

Table 1 Summary of current available guidelines for the use of adjuvant therapy in the treatment of stage I, II, and III typical carcinoid and atypical carcinoid

Stage; Subgroup	Guidelines			
	CommNETS/NANETS	ENETS	NCCN	ESMO
I; TC	Surgery without AT	Surgery without AT	Surgery without AT	Surgery without AT
I; AC	Surgery without AT	Surgery without AT	Surgery without AT	Surgery without AT
II; TC	Surgery without AT	Surgery without AT	Surgery without AT	Surgery without AT
II; AC	Surgery without AT	Surgery without AT	Surgery without AT	Surgery without AT
III; TC	Surgery without AT	Surgery without AT	Surgery without AT	Surgery without AT
III; AC	Surgery without AT	Chemotherapy may be considered in patients with positive lymph nodes	Chemotherapy may be considered. RT is not recommended	Chemotherapy with or without radiation therapy may be considered in patients who are at high risk of relapse, (ex: N2 patients)

AT: Adjuvant therapy; AC: Atypical carcinoid; ENETS: European Neuroendocrine Tumor Society; ESMO: European Society of Medical Oncology; CommNETS: Commonwealth Neuroendocrine Tumour Research Collaboration, NANETS: North American Neuroendocrine Endocrine Tumor Society; NCCN: National Comprehensive Cancer Network; NR: No recommendations; TC: Typical carcinoid.

treatment (5-year OS was 46% for observation *vs* 54% for adjuvant therapy; $P = 0.24$); however, this also did not reach statistical significance[22]. As such, this study lends support to observation following surgery in stage I, II and III TC and stage I, II AC patients. Stage III AC patients had a trend towards improvement but without statistical significance[22].

One study aimed to determine the role for adjuvant therapy in TC alone. Nussbaum *et al*[24] identified 629 patients who had TC with node positive disease; of which, 37 patients (5.9%) were given adjuvant chemotherapy. Observation alone showed a significant survival advantage compared to adjuvant chemotherapy, with 5-year OS being 81.9% for observation *vs* 69.7% for adjuvant therapy ($P = 0.042$). However, after propensity matching, the statistical difference in OS was no longer observed, though a trend towards an increase in 5-year OS in the observation alone cohort was still present (80.9% observation *vs* 69.7% adjuvant therapy; $P = 0.096$). It was concluded by the authors that adjuvant chemotherapy did not improve overall survival among TC patients with node positive disease[24].

Anderson *et al*[25] aimed to determine the role for adjuvant chemotherapy in AC alone. This study identified 363 patients with node negative disease and 218 patients with node positive disease; of these patients, 15 and 89, respectively, received adjuvant chemotherapy. Among the 15 node negative patients who received chemotherapy, OS at 12 mo and 60 mo was 86.7% and 73.3%, respectively, compared to 87.9% and 72.3% among those being observed ($P = 0.54$). Among AC patients with node positive disease who had adjuvant treatment, survival at 12 and 60 mo was 98.9% and 47.9%, respectively, compared with 98.4% and 67.1% survival at 12 and 60 mo, respectively, in those who underwent observation ($P = 0.46$). This study concluded that there was no survival advantage for adjuvant chemotherapy among those with node positive or negative AC[25].

In contrast, three studies lend support for the consideration of therapy after surgery in TC and AC patients[22,26,27]. Unlike the five aforementioned studies that do not support the use of adjuvant therapy, these three studies have a small number of participants, consisting of two single institution retrospective studies[22,26] and one case report[27]. The conclusions of these studies are outlined in Table 2.

Herde *et al*[26] conducted a single institution study describing their use of adjuvant treatment, consisting of either chemoradiation or radiation alone, in 47 TC and 12 AC patients from 1989 to 2009. Of the 59 patients, 55 had surgery and 8 received adjuvant therapy. There were 5 patients (1 TC and 4 AC), who received chemoradiation, 1 AC patient who was node positive received radiation, and 2 AC patients who were found to have metastasis received palliative radiation and palliative chemotherapy. This group found that reserving adjuvant treatment for TC and AC patients with adverse pathologic features was an effective strategy for their patient population. This study reported a 20% recurrence rate among these patients with unfavorable pathological features, which is lower than what has been reported in the literature. Thomas *et al*[28] report that 63.6% of AC patients develop metastasis at a median time of 17 mo after

Table 2 Summary of the available studies examining the use of adjuvant therapy in the treatment of stage I, II, and III typical carcinoid and atypical carcinoid

Study information; Stage and Subgroup	Ref.							
	Westin *et al* [23], 2017	Wegner *et al* [21], 2019	Gosain *et al* [22], 2019	Nussbaum *et al*[24], 2015	Anderson *et al*[25], 2017	Herde *et al* [26], 2018	Chong *et al* [27], 2014	Buonerba *et al*[29], 2010
AT	Chemotherapy	Chemotherapy, radiation or chemoradiation	Chemotherapy	Chemotherapy	Chemotherapy	Chemoradiation or radiation alone	Chemoradiation	Chemotherapy; SSA
Study	Retrospective; NCDB	Retrospective; NCDB	Retrospective; NCDB	Retrospective; NCDB	Retrospective; NCDB	Retrospective; Single Institution	Retrospective; Single Institution	Case Report
Subgroup	TC/AC	TC/AC	TC/AC	TC	AC	TC/AC	TC/AC	AC
Stage	IIB,III	I,II,III	I,II,III	IIB,III	I,II,III	I,II,III	IIB,IIIA	I
Other	node +	NA	NA	node +	Comparing node + and node -	NA	NA	NA
I; TC	NA	Surgery without AT[3]	Surgery without AT	NA	NA	AT in patients with adverse pathologic features[9]	NA	NA
I; AC	NA	Surgery without AT[3]	Surgery without AT[@] (5-yr OS of 84% in obs *vs* 52% AT; $P < 0.01$)	NA	Surgery without AT in node - (OS at 12 and 60 mo in AT 86.7% and 73.3%, *vs* obs 87.9% and 72.3% $P = 0.54$).	AT in patients with adverse pathologic features[9]	NA	Chemotherapy followed by SSA; 10-yr PFS
II; TC	Surgery without AT (inferior OS with AT)[1]	Surgery without AT[3]	Surgery without AT	Surgery without AT[5,6] (5-yr OS 81.9% obs, *vs* 69.7% AT; $P = 0.042$)	NA	AT in patients with adverse pathologic features[9]	chemotherapy may be beneficial in a subset of patients[8]	NA
II; AC	Surgery without AT (no OS benefit)[2]	Surgery without AT[3]	Surgery without AT (5-yr survival of 81% in obs *vs* 55% AT; $P = 0.34$).	NA	Surgery without AT in node +[7]	AT in patients with adverse pathologic features[9]	chemotherapy may be beneficial in a subset of patients[8]	NA
III; TC	Surgery without AT (inferior OS with AT)[1]	Surgery without AT[4]	Surgery without AT	Surgery without AT[5,6] (5-yr OS 81.9% obs, *vs* 69.7% AT; $P = 0.042$)	NA	AT in patients with adverse pathologic features[9]	chemotherapy may be beneficial in a subset of patients[8]	NA
III; AC	Surgery without AT (no OS benefit)[2]	Surgery without AT[4]	Surgery without AT but trend towards benefit (46% in obs *vs* 54% AT; $P = 0.24$)	NA	Surgery without AT in node +[7]	AT in patients with adverse pathologic features[9]	chemotherapy may be beneficial in a subset of patients[8]	NA

[1]Stage IIB, III grouped together and was associated with inferior OS (HR: 3.8; 95%CI: 1.9-7.0; $P = 0.004$).
[2]Stage IIB, III grouped together with no befit in OS (HR: 1.1; 95%CI: 0.68-1.78; $P = 0.6$).
[3]TC and AC stage I and II tumors grouped together to show a median survival of 114 months versus 117 months with observation ($P = 0.30$).
[4]TC and AC stage III tumors favored observation with a median survival of 79 mo *vs* 63 mo ($P = 0.89$).
[5]Adjuvant treatment showed a harmful effect.
[6]When baseline patient features were matched a statistical difference in OS no longer existed but there was a towards detriment (69.7% *vs* 80.9%; $P = 0.096$).
[7]Node + stage II and III grouped together; OS at 12 and 60 mo in AT 98.9% and 47.9%, *vs* obs 98.4% and 67.1%; $P = 0.46$.
[8]Stage IIB and IIIA grouped together; at 2-yr follow up, there was a 28% recurrence rate for those with local regional disease.
[9]Stage I, II, III AC and TC grouped together; overall AT showed a 20% recurrence rate.
AT: Adjuvant therapy; AC: Atypical carcinoid; Obs: Observation; OS: Overall survival; NA: Not applicable; NCDB: National cancer database; PFS: Progression free survival; SSA: Somatostatin analogue; TC: Typical carcinoid.

diagnosis. As such, the authors conclude that adjuvant therapy may be considered in

In a similar study, Chong *et al*[27] conducted a retrospective analysis in their institution between 1990 and 2004 to help elucidate the role of adjuvant treatment in both TC and AC patients. There were 220 TC and 80 AC patients identified who underwent surgery, of which 7 patients with local regional disease (1 patient with TC and 6 with AC; 6 stage IIIA and 1 stage IIB) received adjuvant therapy with platinum and etoposide chemotherapy in combination with radiation. At 2 year follow up, there was a 28% (n = 2) recurrence rate for those with local regional disease. The authors state that for a subset of patients with TC and AC, chemotherapy may be beneficial [27].

Lastly, a case report of a women with surgically resected AC tumor who underwent 6 cycles of carboplatin, etoposide, and epirubicin followed by a somatostatin analog for 10 years demonstrated no evidence of recurrence[29]. Of importance, the tumor was staged as a IB; based on the initial five studies discussed, this patient most likely would have done well without chemotherapy. The major limitation of these three studies is the size of their patient population. While their contribution to the literature is very important, it is difficult to draw sound conclusions from studies with such small numbers.

Taken together, these eight studies indicated that there is no convincing evidence to support the use of adjuvant chemotherapy in stage I, II or III TC and stage I or II AC. Additionally, survival may be compromised if adjuvant therapy is given to this population. With respect to stage III AC, survival benefit was not demonstrated in the literature, despite one large study demonstrating a trend to improved overall survival. Larger, prospective studies are necessary to further consider the role of adjuvant treatment in pulmonary carcinoid tumors. Until then, we caution the utilization of adjuvant treatment in stage I, II, III TC or AC patients.

Small cell lung cancer

Small cell lung cancer (SCLC) has rapid doubling time and is rarely diagnosed at early stages when upfront surgical resection is possible. It is important to rule out occult metastasis with appropriate imaging like CT of the chest, abdomen, and pelvis; PET/CT or bone scans; and MRI of the brain since delaying systemic chemotherapy in patients with metastatic disease can have detrimental outcome. The patients who are surgical candidates require pathologic mediastinal staging to confirm staging. Patients who are then confirmed to have limited stage small cell lung cancer (LS-SCLC), without hilar or mediastinal nodal involvement (TNM stages I-IIA), may be considered for resection of the primary tumor with mediastinal lymph node sampling or dissection. Based on historical phase II clinical trials and observational studies, NCCN and ESMO guidelines recommend that patients without lymph node involvement, confirmed on surgery, receive adjuvant chemotherapy alone and those with unforeseen lymph node involvement should be considered for systemic chemoradiotherapy[30-33]. An analysis of National Cancer Database between 2003-2011 showed that the patients who received adjuvant chemotherapy ± radiotherapy had five-year survival of 53% compared to 40% in those who underwent surgery alone [34]. Other retrospective studies have shown a survival benefit of adjuvant chemotherapy, however, these studies have not been able to show a reduction in recurrence rates[32,35]. Concurrent chemoradiation is preferred over alternating sequential chemotherapy and radiation treatment in the adjuvant setting based on extrapolation of studies among non-surgical LS-SCLC patients showing numeric improvement in survival[36].

Cisplatin-based adjuvant chemotherapy, particularly Etoposide plus cisplatin (EP) for 4 cycles, has been the preferred regimen since 1990s after being shown to have a superior response rates, survival benefit, and improved toxicity profile over conventional alkylator or anthracycline based regimens[37-39]. The EP dosage regimens that has been studied with concurrent or sequential chemoradiotherapy include etoposide 100 mg/m^2 on days 1–3 and cisplatin 75 mg/m^2 on day 1, or etoposide 100 mg/m^2 and cisplatin 25 mg/m^2 on days 1–3 or etoposide 120 mg/m^2 on days 1-3 and cisplatin 60 mg/m^2 on day 1[40,41]. Each cycle is for 21-28 d.

Systematic analysis has shown similar efficacy of carboplatin compared to cisplatin-based regimens. In an analysis of four clinical trials with 663 patients (only 32% with LS-SCLC), comparatively similar number of patients received cisplatin- and carboplatin-based regimens and the outcomes were compared[42]. For the entire cohort, median progression-free survival (mPFS) was 5.5 and 5.3 mo (HR: 1.10; P = 0.25), and median OS was 9.6 and 9.4 mo for cisplatin and carboplatin groups, respectively (HR: 1.08; P = 0.37). As expected, the toxicity profile was different between the groups. However, it must be noted that since the intent is curative in the adjuvant setting and with the absence of prospective trials, carboplatin is only

recommended in patients who have contraindications for the use of cisplatin. The use of myeloid growth factors are also not recommended during concurrent chemoradiotherapy due to the increased risk of thrombocytopenia (and not due to risk of pulmonary toxicity)[43].

The addition of paclitaxel to EP in concurrent chemoradiation regimens has been evaluated in LS-SCLC. However, there is lack of data in the adjuvant setting, and although higher response rates were achieved with the addition of paclitaxel, there was substantial toxicity and lack of significant survival benefit[44,45]. Studies on the use of other agents including antiangiogenic agents and immunotherapy are limited to the non-adjuvant LS-SCLC or ES-SCLC setting.

A highly selected group of patients may be considered for surgical resection after induction chemotherapy, but there is limited data supporting this approach. A phase III randomized controlled trial included 340 patients with LS-SCLC who received 5 cycles of cyclophosphamide, vincristine, and doxorubicin and were determined suitable for resection on restaging[46]. These patients were randomized to thoracic radiation plus prophylactic cranial irradiation with or without surgery. The response rate to chemotherapy was 66%. Median survival was 15.4 mo in the surgical arm compared to 18.6 mo in the non-surgical arm and was not statistically significant (P = 0.78). A smaller phase II trial, however, showed better outcomes with surgery after induction chemotherapy ± radiation[47]. Eight patients with stage IB-IIA underwent 4 cycles of EP and 32 with stage IIB-IIIB received 3 cycles of EP plus thoracic radiation. Both of the groups underwent restaging and 23 underwent complete resection. The pathologic complete response was 34% at surgery. Patients who had an R0 resection had an overall survival advantage over unresected/not completely resected patients (mOS 68 mo *vs* 13 mo; P = 0.01). Similar findings were evident in a retrospective study of 75 patients with stage I-IIIA treated with 3 cycles of EP, 46 of which underwent thoracotomy and 35 had resection done[48]. Four additional cycles of EP were given after surgery. The pathologic complete response rate was 16% and these patient experienced tumor-free survivals of 136+ mo. Among patients who underwent resection, median survival of the cN0-1 subset was 25.09 mo and for cN2 it was 13.75 mo.

Large cell neuroendocrine carcinoma of the lung

With most of the data on adjuvant chemotherapy for LCNEC extrapolated from SCLC trials and other retrospective studies, it is conventionally treated similar to SCLC. It should be noted that large cell carcinoma (LCC) without neuroendocrine differentiation, lacking adenosquamous features, as well as immunohistochemical findings of SCLC, is a diagnosis of exclusion. Electron microscopic and molecular analysis of LCC show that the majority of these cases share features of non-small cell lung cancer and are managed accordingly[4,49].

A nonrandomized prospective study by Iyoda *et al*[50] included 15 patients with LCNEC (Stages I-IV) who received adjuvant chemotherapy with cisplatin 80 mg/m^2 on day 1 and etoposide 100 mg/m^2 on days 1-3 for 2 cycles. Recurrence rate was significantly lower in the adjuvant chemotherapy group compared to historic control (13.3% *vs* 60.87%, P = 0.0065). There was only one death from disease recurrence in the adjuvant group on 5-year follow up. Three patients had grade 4 toxicity, and 10 patients had grade 3 hematologic or gastrointestinal toxicity during treatment.

In a single center retrospective analysis done between 1992 to 2008 with 77 LCNEC and 23 combined LCNEC patients, 24 received induction chemotherapy and 25 adjuvant chemotherapy[51]. Twenty-two of the induction chemotherapy patients received platinum-based combination therapy and 2 received non-platinum single agent chemotherapy. Six patients received etoposide. 68.2% of the patients who received platinum-based combination therapy displayed a partial response, and 31.8% had stable disease. Of the 2 patients who received nonplatinum chemotherapy, 1 had progression of disease and 1 had stable disease. Among the adjuvant chemotherapy group, 20 received adjuvant platinum, and 15 of these received etoposide. Fifteen patients also received adjuvant radiation. 42% of patients received both induction and adjuvant chemotherapy. Stage IA had a 5-year OS of 72% and stage IB 26% (P = 0.0006). The 5-year OS for T1 disease was 66%, T2 44%, T3/4 30%, N0/1 56%, N2/3 24%. There was no association between OS and receipt of induction or adjuvant platinum-based chemotherapy. The 5-year OS was 50% for patients who did not receive chemotherapy compared to 45% for patients who received platinum-based chemotherapy (P = 0.18). However, when restricted to patients with Stage IB-IIIA disease with R0 resection, the 5-year OS was better in patients who received platinum-based chemotherapy as induction or adjuvant treatment compared to those who received other treatments (mOS 7.4 years *vs* 2 years, P = 0.052) with 5-year OS reaching

51% in the platinum-chemotherapy group.

Irinotecan and platinum chemotherapy have also been studied in the adjuvant setting and have not been shown to be superior to EP. The recent Japanese phase III trial among 221 stage I high grade NEC patients (39 patients with SCLC, 38 LCNEC, 14 combined LCNEC and 20 combined SCLC) randomized to EP and IP showed similar PFS[52]. In the LCNEC/combined LCNEC subset, 3-year relapse-free survival was 66.5% for EP *vs* 72.0% for IP (HR = 1.072; 95%CI: 0.517-2.22). Grade 3/4 adverse events were more frequent among the cisplatin-etoposide arm (20% *vs* 4%). There is no available data on other chemoimmunotherapy agents as adjuvant treatment in LCNEC and may be considered in the setting of clinical trials only.

CONCLUSION

Unlike non-small cell lung cancer where adjuvant therapy is well established, adjuvant therapy for NENs of the lung continues to lack prospective trials that definitively guide best treatment options. It is generally well accepted that high grade NENs of the lung (SCLC, LCNEC) that are completely resected should undergo adjuvant therapy. The role of adjuvant therapy in the lower grade TCs and ACs is less well accepted and multiple studies show a detrimental effect and should be avoided outside of a clinical trial. This represents an unmet need in the treatment for NENs of the lung, and prospective studies are warranted.

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