Primary neuroendocrine neoplasms of the lung represent a clinical spectrum of tumors ranging from the relatively benign and slow-growing typical carcinoid to the highly aggressive small-cell lung carcinoma. The rarity of carcinoids has made the role of radiation therapy in their management controversial. This review considers the results of published studies to generate treatment recommendations and identify areas for future research. Surgery remains the standard of care for medically operable disease. Histology plays the most important role in determining the role of adjuvant radiation. Resected typical carcinoids likely do not require adjuvant therapy irrespective of nodal status. Resected atypical carcinoids and large-cell neuroendocrine carcinomas have a significant risk of local failure, for which adjuvant radiation likely improves local control. Definitive radiation is warranted in unresectable disease. Palliative radiation for symptomatic lesions has demonstrated efficacy for all histologies. Collaborative group trials are warranted.

The review by Mackley and Videtic[1] provides an excellent discussion of the appropriate treatment of pulmonary carcinoid in the modern era. Carcinoid tumors have long been considered indolent lesions with a propensity for disseminated disease at diagnosis, generalizing from the behavior of gastrointestinal lesions. Primary pulmonary lesions represent a relatively small percentage of all carcinoid tumors, but are more likely to be clinically localized and appear to be associated with better overall survival than those originating in other sites.[2] Even when considered in the spectrum of pulmonary neuroendocrine tumors (ie, small-cell carcinoma), typical and atypical carcinoids (TC and AC, respectively) are slower-growing, have a lower propensity for nodal metastasis, and confer a relatively favorable prognosis. Advances in tumor staging, including computed tomography (CT), positron-emission tomography (PET), and somastostatin analog immunoscintigraphy, have dramatically increased physician confidence in identifying patients who are free from distant metastases. For all of these reasons, an examination of treatment paradigms for pulmonary carcinoids as a distinct entity is appropriate, as multimodality therapy may provide the means to improve overall survival by optimizing local control. Randomized evidence to guide appropriate therapy for pulmonary carcinoids is lacking and, given the low incidence, such trials are unlikely to be undertaken in the future. Relatively small, single-institution experiences reflect heterogeneous treatment paradigms as well as a spectrum of histologies. This makes critical appraisal of the literature problematic, and requires the judicious application of individualized patient assessment in an experienced multidisciplinary setting.

Key Criteria Three assumptions need to be met to conclude that adjuvant radiotherapy has a role in the treatment of pulmonary carcinoid tumors. First, such tumors must be sufficiently radiosensitive that the dose may be delivered without excess risk of normal tissue toxicity. Second, the risk of local failure must be significant enough that the potential benefit of adjuvant treatment outweighs the potential toxicity. Third, and most important, optimizing local control should reasonably be expected to translate into improvements in either quality of life or survival.

Radiosensitivity and Local Failure
With respect to radiosensitivity, the clinical response of carcinoid tumors has been well established in palliative case series as well as in inoperable patients treated definitively with RT. Partial and complete clinical response rates in TC, AC, and large cell neuroendocrine carcinoma (LCNEC) of up to 87% are substantially better than that seen for epithelial lung carcinoma. The risk of local failure after complete resection is related to histology, nodal involvement, and the extent of invasion of the primary lesion. For completely resected TCs, local failure is relatively uncommon, reported in 7% to 8% of patients in small series. For atypical carcinoids and LCNEC, this risk increases dramatically, up to 20% to 35%. The same risk factors that predict local failure, however, also predict eventual systemic failure. Clearly, in the absence of effective adjuvant systemic therapy, improvements in local control are unlikely to change the ultimate disease course.

Survival Benefit
The published experience describing the survival benefit of adjuvant radiation on resected pulmonary carcinoids is limited, and is well described by Mackley and Videtic. Small, selected, and heterogeneous series make conclusions difficult to draw. Extrapolation of the treatment paradigm for non-small-cell lung cancer (NSCLC) is reasonable, but adjuvant radiation for completely resected NSCLC remains a subject of debate despite thousands of patients, multiple randomized trials, and a controversial meta-analysis.

Newly published retrospective evidence suggests that, in the modern setting, there is a significant survival benefit in NSCLC patients with N2 nodal disease who are treated with adjuvant radiation.[3] An additional, intriguing piece of evidence comes from post hoc analysis of patients who received radiation while enrolled on the Adjuvant Navelbine International Trialist Association (ANITA) trial.[4] Those who were randomized to receive adjuvant chemotherapy derived a greater survival benefit from radiation, implying that reductions in distant recurrence make local control more, and not less, important. These data should be applied to pulmonary carcinoid tumors with appropriate caution, as there is a somewhat lower recurrence risk, as well as a more indolent course, and any potential benefit will be likewise tempered. The clinical response of carcinoid tumors to radiotherapy has been well documented in the palliative setting. This has led to the question of whether adjuvant radiotherapy following complete resection of pulmonary carcinoids would confer any additional benefit. The data to date suggest that local control is improved with this strategy, but no survival benefit has yet been demonstrated. Patients at highest risk, and therefore with the greatest potential benefit, are those with locally advanced primary disease, atypical histology, or nodal metastases. In the setting of meticulous radiographic staging, such patients should be evaluated by a multi-disciplinary team able to weigh the potential risks and benefits of adjuvant local and systemic therapy, on an individual patient basis.

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References:


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