Perspective

Palliative radiotherapy in patients with metastatic non-small cell lung cancer

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Metastatic or stage IV non-small cell lung cancer (NSCLC) is no longer regarded a uniform disease entity even if the general outlook is poor for the vast majority of patients facing this diagnosis. Disease extent is highly variable, and metastatic spread might either be present at initial cancer diagnosis or develop at some point in time after previous curative attempts for stage I-III disease. Selected treatment-naïve patients with limited, resectable intrathoracic tumor and solitary distant metastasis, for example to the brain, experience long-term survival after complete surgery of both primary and metastasis, followed by adjuvant therapy (1,2). However, the majority of patients develop extensive spread, receive palliative systemic treatment, and have a survival expectation of months rather than years. Even in this situation, histological and molecular disease characteristics are crucial determinants of outcome and therapeutic approach. It has for example been shown in a NSCLC brain metastases study that patients with adenocarcinoma histology survived significantly longer than those with other histologies (3). Innovative treatment options including drugs targeting the epidermal growth factor receptor and activated lymphoma kinase pathways have been developed, allowing individually tailored approaches, at least in patients whose tumor cells carry mutations that will render them sensitive to such drugs (4).

Eventually, the disease becomes resistant to any pharmacological treatment attempt. It has long been recognized that patients with NSCLC experience a considerable symptom burden when their disease becomes refractory to a given line of treatment and in the terminal phase. Even if local treatments are unable to control the progress of spread throughout the body, they are highly efficacious in improving symptoms and quality of life. Due to its favourable cost-benefit ratio and well documented palliative benefits, radiotherapy has been a mainstay of multimodal care for decades. However, pattern of practice have shown important variations between physicians and between institutions, raising questions about what should be the preferred timing of radiotherapy delivery and optimum dose-fractionation regimen.

Recently, the Cancer Care Outcomes Research and Surveillance Consortium (CanCORS) studied radiotherapy practice pattern for metastatic NSCLC in several US regions during the time period 2003 to 2005 (5). The demographics of their population correspond well to those of the Surveillance, Epidemiology, and End Results (SEER) population, although the age distribution was slightly younger. The study included 1,574 patients (1,373 had metastatic disease at first diagnosis). Median age was 68 years and median survival 4.7 months. Missing information included extent of disease, performance status and weight loss. Fifty-one percent of these patients received at least one course of chemotherapy after metastatic diagnosis, and 57% had at least one visit with a radiation oncologist. Not all of them were found suitable candidates for palliative radiotherapy. Eventually 87% of those consulting with a radiation oncologist received radiotherapy. The utilization rate was 50% and comparable to the chemotherapy figure of 51%. Among those who received radiotherapy, 67% had one course, 25% had two courses, and 8% had more than two courses during the 15 months follow-up period selected for this study. The most common sites of treatment were

the chest, bone, and brain. However, the study focused on chest and bone metastases irradiation.

In multivariable analysis, only age was significantly associated with use of radiotherapy. Patients older than 80 years had only half the odds of receiving such a treatment as those younger than 55 years of age. Those aged 70-79 years did also experience a reduced likelihood of radiotherapy. Recipients of systemic chemotherapy were more likely to undergo radiotherapy (odds ratio 1.66). In case of bone irradiation, only 6% of patients received a single fraction [the most convenient and cost effective regimen for patients with uncomplicated bone pain, that is no high risk of fracture and no neurological deficits secondary to local extent of the lesion (6)]. Fifty percent received 6-10 fractions. In case of chest irradiation, 42% received more than 20 fractions (about 4 weeks of daily treatment) and less than 30% received no more than 10 fractions. Those receiving chemotherapy, on average, received 7 more fractions and a total added dose of 11 Gy to the chest. In contrast to bone metastases fractionation recommendations, the optimum dose for palliative radiotherapy to the chest is far more controversial. The underlying explanation is the potential to improve survival by moderately higher total doses of radiotherapy, as demonstrated in a combined analysis of several randomized trials (7). However, such doses in the order of 30-42 Gy are typically administered with 10-15 fractions, and only to patients with better survival prognosis. Palliation is less dependent on total dose. For example, a study from the UK randomized patients to receive either 30 Gy in 10 fractions or a 10 Gy single fraction (8). Local symptoms were scored on a physician-assessed, five-point categorical scale and summed to produce a total symptom score (TSS). TSS improved in 77% of patients who received 10 Gy and in 92% of patients who received 30 Gy [a difference of 15% (95% confidence interval 3-28)]. As a consequence of such high rates of symptom improvement with convenient, short-course radiotherapy, even patients with modest survival expectation should be considered for consultation with a radiation oncologist.

In the CanCORS study, it remains unknown how many patients who received radiotherapy in an early setting of the disease versus near the end of life. In a recent study from Nordland Hospital, Bodø, Norway, our group reported that during the last 3 months of life, systemic treatment was given to 28% and thoracic radiotherapy to 23% of patients who died from NSCLC, respectively (9). During the last 4 weeks of life, 27% of the patients received some type of active oncologic therapy, *i.e.* radiotherapy to any site of the body and/or chemotherapy including tyrosine kinase inhibitors. This is in line with other results suggesting that overtreatment, both with regards to treatment indication and, in case of radiotherapy fractionation regimen is a common problem. Data from a recent randomized trial suggested that this problem could be mitigated by implementation of early palliative care in addition to standard oncology treatment (10). Adjusted for age, sex, and performance status, patients in the early palliative care group had half the odds of receiving chemotherapy during the final two months of life (P=0.05). Within 30 days prior to death, chemotherapy was received by 43% (standard care) and 30% of patients (early palliative plus standard care), respectively (P=0.14).

It is crucial to examine key prognostic factors when trying to avoid inappropriate use of chemo- or radiotherapy during the final weeks of life. In one of the large trials 11 poor factors for survival were as follows (hazard ratio in parentheses): skin metastasis (4.49), body mass index less than 18.5 (2.09), increased serum lactate dehydrogenase (1.74), adrenal metastasis (1.52), performance status greater than 0 (1.45), low serum albumin (1.45), men (1.39), bone metastasis (1.39), large cell/not otherwise specified histology (1.29), mediastinal nodal metastasis (1.23) (11). Combined analysis of individual data from 9 randomized trials of second-line treatment in advanced NSCLC suggested that prognosis was significantly influenced by gender (worse in males), performance status, tumor histology (worse in squamous and other histology versus adenocarcinoma), stage (worse in IV versus IIIB), and response to first-line (worse for patients not obtaining objective response) (12).

In conclusion, palliative radiotherapy should be an integral part of multimodal, interdisciplinary management of patients with metastatic NSCLC. The CanCORS study covered the time period 2003 to 2005 and the results might or might not be representative of contemporary practice. It is important to choose wisely from the large number of potential fractionation regimens available in order to prolong survival in the few patients where this is achievable, and avoid overtreatment when pure symptom palliation is the only realistic goal of treatment. Elderly patients should not be deprived from access to palliative radiotherapy, given its minimal toxicity.

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