Accelerated Sequential Radiotherapy and Survival in NSCLC

Written by Emma Hitt Nichols, PhD

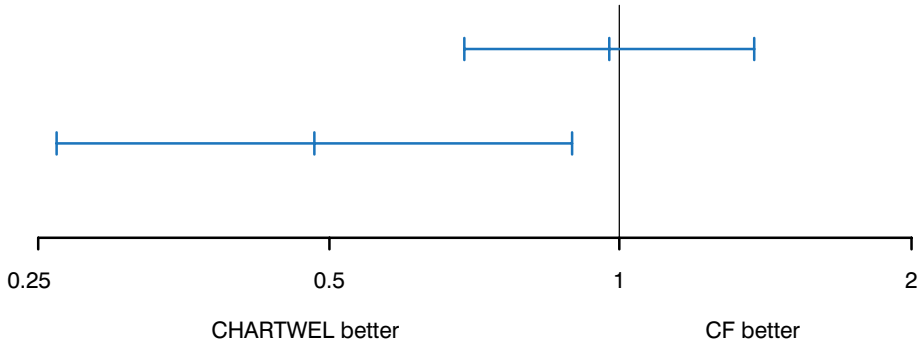
Shorter overall treatment time with radiotherapy (RT) appears to improve outcomes in patients with non–small cell lung cancer (NSCLC) compared with longer overall treatment time. Dirk De Ruysscher, MD, PhD, Leuven Cancer Institute, Leuven, Belgium, outlined optimal RT dose and fractionation for concurrent and sequential schedules for stage III NSCLC.

The dosage and timing of RT affect the local control of NSCLC. For example, when RT is not administered during chemotherapy (CT), longer progression-free survival is achieved with RT that is given for a shorter period of time (<4 weeks) compared with a longer period of time (5 weeks) [Fowler JF et al. *Int J Radiat Oncol Biol Phys* 2004]. A meta-analysis demonstrated that better overall survival is achieved in patients with stages I through III NSCLC when sequential RT is given for a shorter period of time [Mauguen A et al. *J Clin Oncol* 2012].

The dosage and timing of RT are also important in induction CT. Dr. De Ruysscher suggested that long-term survival can be achieved even in patients with large tumor volumes when accelerated RT is administered. In the CHART Weekend Less (CHARTWEL) trial, conventional fractionation that consisted of 66 Gy in 33 fractions for 6.6 weeks was compared with an accelerated, or CHARTWEL, regimen that consisted of 60 Gy in 40 fractions for 2.5 weeks [Baumann M et al. *Radiother Oncol* 2011]. The CHARTWEL regimen resulted in improved outcomes compared with conventional fractionation (Figure 1). However, although greater

Figure 1. Effect of Radiotherapy Dose and Timing on Outcomes of Induction Chemotherapy in NSCLC

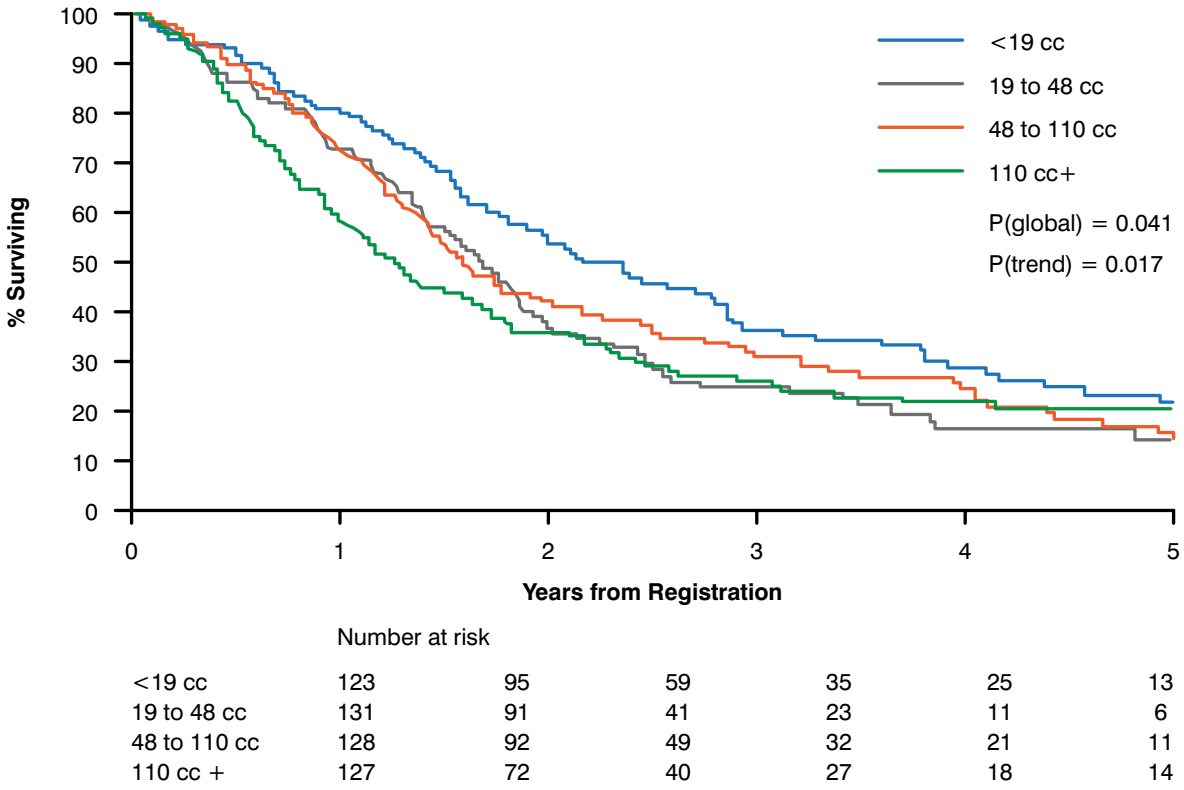
Ctx	CF	CHARTWEL	HR	p Value
No	103/150	96/150	0.97 (0.69; 1.37)	0.86
Yes	38/53	36/53	0.48 (0.26; 0.89)	0.019



CF=controlled fractionation; CHARTWEL=CHART Weekend Less; Ctx=chemotherapy; NSCLC=non–small cell lung cancer.

Reproduced from Baumann M et al. Final results of the randomized phase III CHARTWEL-trial (ARO 97-1) comparing hyperfractionated-accelerated versus conventionally fractionated radiotherapy in non–small cell lung cancer (NSCLC). *Radiother Oncol.* 2011;100(1):76-85. With permission from Elsevier.

Figure 2. Effect of Tumor Volume on Survival With Accelerated Radiotherapy



Number at risk

<19 cc	123	95	59	35	25	13
19 to 48 cc	131	91	41	23	11	6
48 to 110 cc	128	92	49	32	21	11
110 cc +	127	72	40	27	18	14

Reproduced from Ball DR et al. The complex relationship between lung tumor volume and survival in patients with non–small cell lung cancer treated by definitive radiotherapy: a prospective, observational prognostic factor study of the Trans-Tasman Radiation Oncology Group (TROG 99.05). Radiother Oncol. 2013;106(3):305-311. With permission from Elsevier.

tumor volume is associated with greater local failure when conventional fractionation is given, this appears to not be the case with accelerated fractionation (the CHARTWEL regimen). Similarly, in the Trans-Tasman Radiation Oncology Group 99.05 trial, tumor volume was not associated with survival at 4 years in patients who received 50 Gy in 20 fractions, despite initial differences in survival (Figure 2) [Ball DL et al. *Radiother Oncol* 2013].

Concurrent CT and RT are considered better than sequential CT and RT, according to level I evidence. A meta-analysis demonstrated that concurrent CT and RT results in better outcomes compared with sequential therapy across many trials [Auperin A et al. *J Clin Oncol* 2010]. A Phase 3 trial compared 60 to 66 Gy in 2 Gy/d fractions for 6 to 7 weeks with 66 Gy in 24 fractions for >5 weeks, both of which were concurrent with CT (cisplatin and etoposide, cisplatin and vinorelbine, or cisplatin alone). All of these regimens had similar efficacy. Dr. De Ruysscher suggested that in the future, clinical trials should compare concurrent CT and RT with sequential RT given at a higher biologic dose.

In concurrent chemoradiotherapy, the dose of radiation given is important. It is generally thought that the higher the dose of radiation, the better the efficacy. However, Dr. De Ruysscher highlighted the surprising findings of a trial that compared 60 Gy for 6 weeks with 74 Gy for 7.5 weeks. Interestingly, at 18-month follow-up, the survival rate and median overall survival were 53.9% and 19.5 months, respectively, in patients who received 74 Gy and 66.9% and 28.7 months, respectively, in patients who received 60 Gy (p=0.0007). In addition, the 74-Gy dose resulted in a significantly greater local progression rate (p=0.0319) and trended toward worse distant failure (p=0.1576) compared with the 60-Gy dose. An ongoing trial will provide further information regarding the effect of the dose of RT with concurrent CT (NCT1486602). This open-label, dose-escalation,

Phase 1 trial of patients with NSCLC will evaluate paclitaxel and carboplatin plus hypofractionated RT, or paclitaxel plus carboplatin after RT is completed. The primary outcome is the maximum tolerable RT dose fraction in the concurrent arm.

Dr. De Ruysscher concluded by stating that in his opinion, the most optimal nonconcurrent RT at this time is using an accelerated schedule. For concurrent chemoradiotherapy, the standard regimen should be retained at this point, as decreasing the overall treatment time with RT has not yet been demonstrated to improve outcomes.

Stereotactic Body Radiation Therapy: Approaches in Early-Stage NSCLC

Written by Emma Hitt Nichols, PhD

Stereotactic body radiation therapy (SBRT) is effective in patients with early-stage non–small cell lung cancer (NSCLC) who are either medically inoperable or high-risk operable. Krzysztof Konopa, MD, Medical University of Gdańsk, Gdańsk Poland, discussed treatment approaches and considerations for the use of SBRT in this population.

The standard of care for patients with early-stage NSCLC is surgical resection; however, more than 20% of patients cannot undergo surgery due to comorbidities, and 30% of patients do not undergo surgery in the United States [Cykert S et al. *JAMA* 2010].

SBRT is effective in patients with medically inoperable NSCLC. In a Phase 2 trial of patients with inoperable NSCLC, the 3-year estimated overall survival (OS) rate was 59.5%, and the lung cancer–specific survival rate was 88.4% [Baumann P et al. *J Clin Oncol* 2009]. In the Radiation Therapy Oncology Group (RTOG) 0236 Phase 2 trial of patients with inoperable NSCLC, OS was more than 50% and disease-free survival (DFS) was about 50% [Timmerman R et al. *JAMA* 2010]. Similarly, in the medically inoperable arm of the Japan Clinical Oncology Group (JCOG) 0403 Phase 2 trial, the 3-year OS rate was 59.9% (95% confidence interval [CI], 51.4% to 67.5%), and the 3-year local control rate was 88% [Nagata Y et al. *Int J Radiat Oncol Biol Phys* 2012].

SBRT may also be effective in patients who have early-stage NSCLC and are at high risk for surgery. In a retrospective study comparing SBRT to wedge resection, OS was greater in patients who underwent wedge resection, whereas SBRT resulted in better local control and freedom from failure [Grills IS et al. *J Clin Oncol* 2010]. In a population-based matched-pair comparison, OS was greater in patients who received SBRT until about 24 months; OS was greater at 36 months in patients who underwent resection [Palma D et al. *Radiother Oncol* 2011]. In another retrospective study, SBRT resulted in improved OS compared with surgery, but regional control and cancer-specific survival were similar among both arms [Robinson CG et al. *J Thorac Oncol* 2013]. A Surveillance, Epidemiology, and End Results (SEER)–Medicare retrospective analysis found that the rate of OS was greatest in patients who underwent lobectomy, followed by sublobar resection, SBRT, conventional radiation, and no treatment [Shrivani SM et al. *Int J Radiat Oncol Biol Phys* 2012].

Prof. Konopa stated these data indicate that the efficacy of SBRT is consistent among studies, with 3-year rates of tumor control of 85% to 90%, rates of OS of 50% to 60% in medically inoperable patients, and 76% for high-risk operable patients.

Patients with large NSCLC tumors also benefit from SBRT. In a retrospective analysis, patients with stage T2 to T4 NSCLC with a planned target volume (PTV) of ≤106 demonstrated a significant increase in local failure-free survival compared with patients with a PTV >106 (log-rank p=0.05). However, there is a risk of symptomatic pneumonitis, particularly in patients with an internal target volume (ITV) of ≥145 cc, and those who receive a contralateral mean lung dose of ≥3.6 Gy [Bongers EM et al. *Radiother Oncol* 2013]. Dr. Konopa stated that although SBRT for large tumors appears to be effective for local control, there is still a risk of distant failures and symptomatic pneumonitis. Therefore, additional studies are needed to determine if SBRT is beneficial in this population.

Prof. Konopa stated he thinks the data suggest that SBRT should be standard therapy for medically inoperable NSCLC, and it is comparable to surgery in patients with early-stage NSCLC who are considered at high risk for surgery, such as elderly patients.