



# Locally Advanced Non-Small Cell Lung Cancer: Whether Higher Dose of Radiation is a Winner?

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## Editorial

Radiotherapy is a mainstay of treatment of locally advanced Non-Small Cell Lung Cancer (NSCLC). Despite that there is a relative paucity of prospective trials directed on the radiotherapy use in this indication in comparison with prospective studies related to the use of chemotherapy. In this context, a recently published randomized study by [1], is certainly to be welcomed. This randomized phase II trial (NARLAL: Navelbine and Radiotherapy in Locally Advanced Lung cancer) compared two commonly used radiation dose schedules 60 Gy in 30 fractions (60 Gy/30F) and 66 Gy in 33 fractions (66 Gy/33F) based on a “pick the winner” design. Radiotherapy was given concomitantly with a convenient oral formulation of Vinorelbine administered 50 mg three times weekly. Radio-chemotherapy was preceded by two cycles of full-dose induction chemotherapy Carboplatin and oral Vinorelbine. After demonstration that plan of 66 Gy/33F (with 3-dimensional conformal technique or IMRT at the discretion of treating institution) may fulfill predefined dose constraints criteria patients were randomized to 60 Gy or 66 Gy. All patients had FDG-PET CT performed as a part of initial work-up and at nine months of follow-up as part of the protocol. The primary end-point of this study was Local Progression Free Interval (LPFI). Local failure was defined as a progression within radiation field. Overall Survival (OS) was a secondary endpoint. Of 121 patients included, three were not able to receive 66 Gy/33F, because of dose constraints, one had distant metastases at the inclusion, thus finally 117 stage IIB and III NSCLC cases were considered eligible and were subject to the analysis. The LPFI at 9 months was 54% and 59% for 60 Gy/30F and 66 Gy/33F arms, respectively ( $p = 0.55$ ). The median OS was also not different for compared groups, 23.3 months for 60 Gy/30F and 23.7 months for 66 Gy/33F. Toxicity in this trial, partially earlier published in detail [2], was mild and not statistically different in compared schedules. Based on the complex “pick the winner” study design, the 66 Gy/33F was chosen as a winning arm for further phase III studies that will test further dose escalation given as a simultaneous boost to the areas of high FDG uptake within tumor and pathological lymph nodes with a standard arm of 66 Gy/33F concurrently with doublet platinum based chemotherapy [3].

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Although this trial as acknowledged also by the authors was not ideal because of debatable treatment schedule (the use of radio sensitizing monotherapy instead of doublet platinum based chemotherapy for fit patients and the use of induction chemotherapy) which reflected more local habits than evidence based recommendations [4], we may still learn a lot from this trial because of the high quality of prospectively gathered data.

First of all, there is the issue of the use of 60 Gy/30F in comparison with 66 Gy/33F. Dose-response curve in radiotherapy for lung cancer has a sigmoidal shape what means that the probability of local control increases with the increase of radiation dose [5]. However, higher dose may cause additional toxicity which compromises benefit of dose escalation. Recently, it was demonstrated in the randomized study that dose escalation in conventionally fractionated radiotherapy concomitant with chemotherapy from standard dose of 60 Gy in 30 fractions to 74 Gy in 37 fractions was detrimental for OS; median OS in the standard dose group was 28.7 months and 20.3 months in the escalated dose group,  $p = 0.004$  [6]. There are several probable reasons of the decreased survival with dose escalation above 70 Gy; underreported toxicity, lower local control due to inadequate target coverage in high-dose arm or prolongation of treatment time with higher total dose. However, in the lower range of doses, higher dose revealed to be beneficial. RTOG 73-01 phase III trial randomized patients with NSCLC to 40, 50, or 60 Gy in 2 Gy fractions. Local control improved with higher dose and three-year local control rates were 52%, 62%, 73% for 40, 50, and 60 Gy groups, respectively,  $p = 0.02$  [7]. Thus a dose of 60 Gy in 30 fractions became a recommended dose for radical radiotherapy for NSCLC. In the RTOG 73-01 trial, no dose in homogeneity correction was used what means in practice that in the thoracic region the actual target absorbed dose exceeded the prescribed

dose by up to 15 percent [8]. For this reason, with introduction of dose in homogeneity corrections algorithms for treatment planning that made dose calculation more accurate, the dose schedules of 66 Gy/33F became also a standard dose for radical radiotherapy in many countries. The standard dose arm in CHARTWEL trial may serve as an example of the successful use of the 66 Gy/33F schedule [9]. On the other hand, many radiotherapy trials for NSCLC with concurrent chemotherapy were still using 60 Gy/30F as a standard arm [10]. Such a radiation schedule of 60 Gy/30F was also used in the phase I study that established a dose level for oral Vinorelbine used in the NARLAL trial [11]. In this context [10]. Concept of conducting a study with a goal of selecting a radiation dose schedule of 60 Gy/30F or 66 Gy/33F as a standard dose for further testing of dose escalation was justified. Only 3 out of 121 patients with locally advanced NSCLC were not able to get 66 Gy/33F due to dose constraints. Authors consequently realized their project and showed that indeed 66 Gy/33F given for NSCLC does not result in higher toxicity. Local control and OS were similar. Even, as for many practitioners that are commonly using 66 Gy/33F such a trial may seem odd in this regard, for many others that are still giving 60 Gy/30F the results of this trial may be convincing and lead to the change of their practice. Once more this was shown that increasing a radiation dose within a commonly accepted in radiation oncology range as in this case from 60 to 66 Gy is safe. However, a question remains what about a further dose escalation and does it matter to develop this concept in the light of recently demonstrated in RTOG 0617 trial a detrimental effect of conventionally fractionated dose of 74 Gy [5]. Alternative ways of dose escalation may be warranted, as a planned NARLAL2 dose per fraction escalation study, in which investigators from the presented NARLAL trial will compare 66 Gy/33F with dose heterogeneously escalated to the FDG-PET avid volumes, with mean doses up to 95 Gy/33 fractions and 74 Gy/33 fractions to the escalated volumes in the tumor and malignant lymph nodes, respectively [11]. Such an approach has for a rationale a concept that shortening of treatment time may be beneficial and hypo fractionation using modern treatment technologies is safe. This may be supported by the recently published long-term results of the Reditux trial on 102 patients, in which the exceptionally long median OS of 31.5 months was obtained in hypo fractionated accelerated radiotherapy schedule (66 Gy in 24 fractions). Five-year OS rate was 37% in this trial [12]. Secondly, the study by Hansen et al. [1] brings robust data on the outcome of contemporarily treated locally advanced NSCLC patients with standard dose conventionally fractionated radiotherapy. Despite a suboptimal chemotherapy regimen used in this study, median OS was 23.5 months, higher than in older completed about 10-20 years ago radiotherapy trials, in which OS after radical radiotherapy or radio-chemotherapy trials was almost always lower than 20 months [10]. Recently, this is always higher than 20 months, and often approaching 30 months. In a standard dose arm 60 Gy/30F in the RTOG 0617 trial that used concomitant full dose chemotherapy a median OS was 28.7 months [6]; in SOCCAR trial with either sequential or concurrent chemotherapy and accelerated hypo fractionated radiotherapy 55 Gy in 20 fractions OS was 27.4 months [13]; in INDAR trial of radio-chemotherapy using individualized accelerated (partially hyper fractionated) radiotherapy to median dose of 65 Gy, stage IIIA patients had median OS of 26 months [14]. This indicates the progress of the last decade made in radiotherapy techniques, advances in diagnostics and supportive care.

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