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LETTER TO THE EDITOR

**Tumor size does not predict pathological complete response rates after pre-operative chemoradiotherapy for non-small cell lung cancer**

CORNELIS G. VOS<sup>1</sup>, MAX DAHELE<sup>2</sup>, CHRIS DICKHOFF<sup>1</sup>, SURESH SENAN<sup>2</sup>, ERIK THUNNISSEN<sup>3</sup> & KOEN J. HARTEMINK<sup>1</sup>

<sup>1</sup>Department of Surgery, VU University Medical Center, Amsterdam, The Netherlands, <sup>2</sup>Department of Radiation Oncology, VU University Medical Center, Amsterdam, The Netherlands and <sup>3</sup>Department of Pathology, VU University Medical Center, Amsterdam, The Netherlands

**To the Editor,**

Patients with locally advanced (LA) non-small cell lung carcinoma (NSCLC) and a large primary tumor are at risk of being considered to have incurable disease or excluded from radical-intent treatment [1,2]. We generally consider radical chemoradiotherapy in eligible patients so long as the risk of toxicity appears acceptable – absolute tumor size is not used to allocate treatment. We decided to test the hypothesis that even large tumors can respond well to chemoradiotherapy. We studied superior sulcus tumors (SST), considered a subgroup of NSCLC, because patients with operable SST receive induction chemoradiotherapy followed by resection. This allowed us to use pathological complete response (pCR), which has been correlated with survival, as an objective, clinically meaningful end-point of treatment response [3–6]. At the same time we also tested the hypothesis that large tumors could be sterilized with modest doses of radiotherapy (45–50 Gy).

**Patients and methods**

*Patients and treatment*

This retrospective study was performed with institutional approval. Patients treated between 2002 and 2011 were eligible if, 1) they had a diagnosis of SST and received trimodality therapy, 2) 45–50 Gy radiotherapy was delivered in our institution, and 3) the primary tumor was completely imaged on a radiotherapy planning computed tomography (CT) scan. Standard induction chemoradiotherapy was

three cycles of full-dose platinum-based chemotherapy and CT-planned, image-guided, conformal radiotherapy starting with cycle 2 [7]. Patients without disease progression were usually operated on 4–6 weeks after induction therapy.

*Histopathological examination*

The resection specimen underwent histopathological examination for vital tumor cells. During initial gross examination of the resection specimen, at least two blocks were taken from the tumor area and two from the adjacent lung. Starting in 2008, if vital tumor cells were not identified in these blocks then the remainder of the surgical specimen was embedded in paraffin and sectioned for further examination.

*Tumor size measurements*

The radiotherapy planning CT scan was typically performed within one to two weeks of the start of the first cycle of chemotherapy. When the planning CT was respiratory-correlated (4-dimensional), then the end-inspiration phase was used. The maximum axial and cranio-caudal tumor diameters were measured in Centricity RA 600 6.1 (GE Medical Systems, USA) with a 65" high-definition 1080p plasma display (Panasonic TH-65PF11, Panasonic Corporation, Osaka, Japan) and simultaneously reviewed by four authors.

*Volumetric analysis*

The primary tumor was contoured in VelocityAI 2.7.1 (Velocity Medical Solutions, Atlanta, Georgia,

Correspondence: C. G. Vos, VU University Medical Center, Department of Surgery, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands. Tel: +31 204444400. Fax: +31 204444512. E-mail: c.vos@vumc.nl

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USA) by one author and reviewed by a second in order to derive the gross tumor volume (GTV). Tumor-soft tissue interfaces were contoured using mediastinal window settings and for tumor-lung interfaces, additional information was obtained from lung window settings.

### Statistical analysis

Statistical analyses were performed using SPSS, version 17.0 (SPSS, Inc., Chicago, IL, USA). The Pearson correlation coefficient ( $R^2$ ) was used to describe correlations. To explore if tumor size measurements could predict pathological response, size variables were entered in a stepwise backward logistic regression analysis using a cut-off value of  $p = 0.05$ . Odds ratios (OR) were presented with 95% confidence intervals if statistically significant predictors were identified. In addition receiver operating characteristic (ROC) curves were used to determine the ability of bi-dimensional tumor size and GTV to predict pCR. An area under the curve (AUC) approaching 1 indicated perfect discrimination. Pearson's  $\chi^2$ -test was used to compare groups for occurrence of pCR. The Mann-Whitney test was used to compare groups for continuous variables. Statistical significance was defined as  $p < 0.05$ .

## Results

### Patient characteristics

Between January 2002 and December 2011, 84 patients with a SST received trimodality treatment and 43 had planning scans for radiotherapy at our institution. Six patients were excluded because the radiotherapy dose was either 39 ( $n = 4$ ) or 66 Gy ( $n = 2$ ). One patient was excluded because atelectasis around the tumor did not allow for accurate tumor delineation. This left a total of 36 patients. The median interval between start of induction chemotherapy and the planning CT scan was 12 days (range, 1–35 days). Patient characteristics are summarized in Table I.

### Tumor size and pathological complete response

Of the 36 eligible patients, 12 (33%) had a pCR after induction therapy. The maximal axial tumor diameter ranged from 40–123 mm, cranio-caudal diameter ranged from 28–133 ml, and gross tumor volume ranged from 20–750 ml. Median maximum axial diameter was 64 mm (range, 36–123 mm) for patients with a pCR and 64 mm (range, 40–107 mm) for patients without a pCR. Median cranio-caudal diameter was 54 mm (range, 30–133 mm) and 66 mm (range, 28–113 mm) for patients with and without a

Table I. Patient characteristics.

Characteristic	n (%)
N	36
Age [years, (range)]	55 (39–74)
Sex	
Male	19 (53%)
Female	17 (47%)
Histology	
Squamous cell	7 (19%)
Adenocarcinoma	23 (64%)
Large cell	6 (17%)
Radiotherapy dose:	
45 Gy	2 (5%)
46 Gy	6 (17%)
50 Gy	28 (78%)

pCR, respectively. Median GTV for patients with a pCR was 50 ml (range, 20–250 ml) compared with 104 ml (23–382 ml) for patients without a pCR. No significant differences were seen in tumor measurements between patients with and without a pCR.

A strong correlation was observed between maximum axial diameter and GTV ( $R^2 = 0.86$ ,  $p < 0.001$ ) and cranio-caudal diameter and GTV ( $R^2 = 0.86$ ,  $p < 0.001$ ). Logistic regression analysis demonstrated that neither maximum axial diameter, nor cranio-caudal diameter or GTV were predictive for pCR. The area under the ROC-curve for prediction of pCR was 0.41 ( $p = 0.45$ ) for maximum axial diameter, 0.39 ( $p = 0.37$ ) for cranio-caudal diameter and 0.33 ( $p = 0.15$ ) for GTV.

The study population was divided in two groups with values below and above the median (small and large tumors, respectively) for the maximum axial diameter (65 mm), cranio-caudal diameter (62 mm) and GTV (86 ml). For small tumors, a pCR was achieved in seven of 19 (36.8%), six of 19 (31.6%), and seven of 13 (53.8%) patients for maximum axial diameter, cranio-caudal diameter and GTV, respectively. For large tumors, this was five of 17 (29.4%), six of 17 (35.3%) and three of 13 (23.1%), respectively. These differences were not statistically significant ( $p = 0.64$ ,  $p = 0.81$  and  $p = 0.11$ , respectively). The median interval between start of induction chemotherapy and the planning CT scan was 11 (range, 1–19) days for large tumors and 13 (range, 1–35) days for small tumors.

## Discussion

These data, from a cohort of patients with superior sulcus tumors who were managed with trimodality therapy, show that large tumor size or volume near the beginning of induction chemoradiotherapy does not preclude a complete pathological response. This supports the hypothesis that even large tumors can

respond well to chemoradiotherapy. The data also demonstrate that even modest radiation doses delivered concurrently with full-dose chemotherapy can be effective in large tumors. These findings are strengthened by reports that on univariate analysis tumor size does not appear to be a key determinant of prognosis after chemoradiotherapy for locally-advanced NSCLC and that long-term survival is possible in some patients with larger tumors [8,9].

We acknowledge potential limitations of the study. For example, the inclusion criteria and retrospective design may have resulted in selection bias; there was some variation in the timing of the baseline CT scan; we have not assessed patient survival and we have used SST as a model for NSCLC. Finally the relatively small size of the study limits the strength of the conclusions that can be drawn. Nonetheless, the results are suggestive that size alone should not be the deciding factor in whether or not to offer appropriately selected patients radical-intent treatment. They also highlight the need for better means of predicting treatment response and prognosis in patients with LA-NSCLC, irrespective of tumor size.

**Declaration of interest:** The VU University Medical Center Department of Radiation Oncology has research collaborations with Velocity Medical Solutions and GE.

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