Chapter 7

Tumor cavitation in patients with stage III non-small-cell lung cancer undergoing concurrent chemoradiotherapy: Incidence and outcomes

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Abstract

Introduction: Commonly reported complications after concurrent chemoradiotherapy (CCRT) in patients with stage III non-small-cell lung cancer (NSCLC) include febrile neutropenia, radiation esophagitis, and pneumonitis. We studied the incidence of tumor cavitation and/or “tumor abscess” after CCRT in a single-institutional cohort.

Methods: Between 2003 and 2010, 87 patients with stage III NSCLC underwent cisplatin-based CCRT and all subsequent follow-up at the VU University Medical Center. Diagnostic and radiotherapy planning computed tomography scans were reviewed for tumor cavitation, which was defined as a nonbronchial air-containing cavity located within the primary tumor. Pulmonary toxicities scored as National Cancer Institute Common Toxicity Criteria v3.0 of grade III or more, occurring within 90 days after end of radiotherapy, were analyzed.

Results: In the entire cohort, tumor cavitation was observed on computed tomography scans of 16 patients (18%). The histology in cavitated tumors was squamous cell (*n* = 14), large cell (*n* = 1), or adenocarcinoma (*n* = 1). Twenty patients (23%) experienced pulmonary toxicity of grade III or more, other than radiation pneumonitis. Eight patients with a tumor cavitation (seven squamous cell carcinoma) developed severe pulmonary complications; tumor abscess (*n* = 5), fatal hemorrhage (*n* = 2), and fatal embolism (*n* = 1). Two patients with a tumor abscess required open-window thoracostomy post-CCRT. The median overall survival for patients with or without tumor cavitation were 9.9 and 16.3 months, respectively ($p = 0.09$).

Conclusions: With CCRT, acute pulmonary toxicity of grade III or more developed in 50% of patients with stage III NSCLC, who also had radiological features of tumor cavitation. The optimal treatment of patients with this presentation is unclear given the high risk of a tumor abscess.

Introduction

Concurrent chemoradiotherapy (CCRT) is considered to be the standard of care for fit patients who present with a stage III non-small-cell lung cancer (NSCLC).[1] The survival gains observed with CCRT relative to the sequential administration of both modalities have been attributed to improved loco-regional tumor control.[2] Increased toxicity observed with CCRT includes acute esophagitis and neutropenia, with grade III/IV neutropenia reported in range of 32% to 43% of patients treated using cisplatin-etoposide and concurrent radiotherapy.[3–5] A retrospective analysis of late complications after CCRT to 66 Gy or higher, reported pulmonary complications including bronchial stenosis and fatal hemoptysis but neither tumor cavitation nor fatal infections were mentioned.[6]

About 10% to 20% of all lung carcinomas present with radiological cavitation, which is believed to be due to tumor necrosis as a consequence of ischaemia and/or bronchial obstruction.[7] Earlier reports had observed that cavitated tumors undergoing treatment with chemotherapy and/or radiotherapy could result in potentially "serious, difficult-to-treat infectious complications."[8,9] Awareness of tumor cavitation has increased since this finding was linked to the toxicity and efficacy of antiangiogenic agents in NSCLC.[10,11]

CCRT has been our routine treatment strategy for stage III NSCLC since 2003.[12] After encountering isolated cases of cavitation developing in such, we evaluated the incidence, treatment, and outcome of tumor cavitation in consecutive patients with stage III NSCLC who underwent CCRT with cisplatin-based chemotherapy and concurrent thoracic radiotherapy, between 2003 and 2010.

Patients and methods

Patients treated at our institution were eligible for the present retrospective analysis if all baseline and follow-up imaging, and the complete details on pulmonary toxicity and follow-up imaging were available. Between 2003 and 2010, a total of 243 patients with stage III NSCLC underwent treatment with cisplatin-based CCRT, including 22 patients who were treated in a phase II trial conducted between 2005 and 2006.[13] Of these 243 patients, we excluded 71 who underwent surgery after induction CCRT. Also excluded were 85 patients who underwent radiotherapy at our center, but whose systemic chemotherapy and radiological follow-up was performed at other referral hospitals. The remaining 87 patients with a stage III NSCLC are the subject of this report because all imaging, chemotherapy, and follow-up were conducted at our center after definitive CCRT.

Details of the treatment scheme for patients treated outside trials have been described previously, and eligibility was mainly based on fitness to receive full-dose cisplatin-based chemotherapy, as well as the percentage volume of lung tissue receiving a dose of 20 Gy or more (V_{20}).[12] The chemotherapy schedule consisted of a cycle of induction cisplatin 80 mg/m^2 on day 1, and gemcitabine 1250 mg/m^2 on days 1 and 8, followed by cisplatin 80 mg/m^2 (days 21 and 42) and etoposide 100 mg/m^2 (days 21–23 and 42–44) during concurrent thoracic radiotherapy. Involved-field radiotherapy commenced on day 22, with a minimum dose of 46 Gy upto 66 Gy in 2 Gy-fractions (5 days/week). The remaining 22 patients with stage III NSCLC were treated with CCRT in a phase II trial,[13] receiving weekly cisplatin and docetaxel on days 1, 8, 15, 22, 29, and 36 at a dose of 20 mg/m^2. Radiotherapy commenced on day 1 in once-daily fractions of 1.8 Gy to a maximum dose of 59.4 Gy.

All diagnostic and radiotherapy planning computed tomography (CT) scans before the start of CCRT were reviewed by two authors (EP and SS) for tumor cavitation, which was defined as an air-containing cavity within the primary tumor and which was not identifiable as an airway. At the time these patients were treated, the institutional policy was not influenced by the presence of cavities in the tumor. Subsequently, patient/treatment characteristics, details of pulmonary toxicity of grade III or more (National Cancer Institute Common Toxicity Criteria v3.0) within 90 days after the end of radiotherapy, and follow-up data were derived from an institutional database. Progression-free and overall survival was calculated using the Kaplan-Meier method and calculated from start of chemotherapy to September 2, 2011. Results are presented as median and range or number and percentage. A *p* value less than 0.05 was considered statistically significant.

Results

Incidence of tumor cavitation and survival

Characteristics of the 87 eligible patients are summarized in **Table 1**. Sixteen patients (18%) had a cavity in the primary tumor before the start of CCRT, with maximal cavity diameters ranging between 0.5 and 4.5 cm. In this patient group, the histology was squamous cell carcinoma (SCC) (*n* = 14), adenocarcinoma (*n* = 1), or large-cell undifferentiated carcinoma (*n* = 1). The CT images showing individual tumor cavitations from six patients are presented in **Appendix 1**. All but three patients with tumor cavitation, completed their planned chemotherapy, and received a minimal radiotherapy dose of 46 Gy. Median overall survival for all 87 patients was 15.2 months, and for patients with or without tumor cavitation, the corresponding values were 9.9 and 16.3 months, respectively (log-rank $p = 0.09$) (**Figure 1**). Survival for patients with SCC and other histologies did not differ significantly (log-rank $p = 0.273$). Among patients who did not have pretreatment tumor cavitation, two subsequently developed a cavitation in the tumor within 3 months of completing CCRT. In addition, three more patients developed pulmonary cavitations in the setting of a postobstructive pneumonia.

Pulmonary toxicity of grade III or more, and follow-up of patients

Eight of 16 patients (50%) with pretreatment tumor cavitation developed acute pulmonary toxicity of grade III or more, other than radiation pneumonitis, as opposed to only 12 of 71 (17%) in those without tumor cavitation. **Table 2** summarizes details of all 20 patients developing acute pulmonary toxicity of grade III or more. Two patients with large cavitated tumors died of massive pulmonary hemorrhage 1 month after start of the treatment. Another patient died 2 weeks after the end of radiotherapy (46 Gy) from pulmonary embolism. Infection, presenting as an air-fluid level in the tumor cavitation (tumor abscess) on radiological imaging, was observed in the five remaining patients. Of these, one patient was hospitalized and treated with intravenous (IV) administration of antibiotics during CCRT, but died shortly after treatment. The other four were hospitalized 10, 13, 21, and 87 days, respectively, after the end of radiation treatment. Of the latter, two patients recovered after IV administration of antibiotics, and subsequently developed intrathoracic disease progression after 18.5 and 27 months.

Table 1. Patient and treatment characteristics (n=87)

Characteristic	Patients
Sex	
Male	61 (70%)
Female	26 (30%)
Age (yrs)	
Median (range)	60 (42-80)
Clinical staging	
Stage IIIA	36 (41%)
Stage IIIB	51 (59%)
Histology	
Squamous-cell carcinoma	37 (43%)
Adenocarcinoma	28 (32%)
Large-cell carcinoma	22 (25%)
Maximum size of primary tumor (n=83)	
All tumors (median)	6 cm
Squamous-cell carcinoma (median)	7 cm
Percentage of tumors ≥8 cm	26 (30%)
Concurrent chemotherapy	
Cisplatin-etoposide (3-weekly)	75 (86%)
Cisplatin-docetaxel (weekly)	12 (14%)
Total radiation dose (Gy)	
<60	38 (44%)
60	21 (24%)
>60	28 (32%)
Leucocytopenia grade ≥III (n)	
Squamous-cell carcinoma	25
Nonsquamous-cell carcinoma	29
Radiation pneumonitis*	
Grade II	13
Grade III	4

* scored according to National Cancer Institute Common Toxicity Criteria v3.0.

Table 2. Characteristics of patients with grade ≥III acute pulmonary toxicity (n=20)

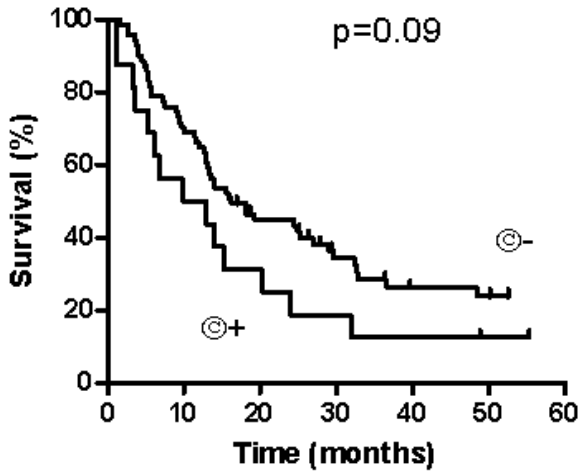
Sex	TNM Stage	Histology	Primary location	Maximal tumor Ø (cm)	CCRT Schedule[a]	Radiation dose (Gy)	WBC toxicity (max grade)	Acute pulmonary toxicity	Grade toxicity	Interval start treatment – event (days)	Survival (m)
♀	T4NxM0 IIIB	SCC	Central [b]	13	1	6	2	Hemorrhage	5	32	1.1 [c]
♂	T3N2M0 IIIA	SCC	Peripheral [b]	12	2	29	0	Hemorrhage	5	33	1.1 [c]
♂	T4NxM0 IIIB	SCC	Central [b]	10	1	46	1	Embolism	5	98	3.3 [c]
♀	T3N2M0 IIIA	Large-cell	Central	10	1	60	3	Embolism	3	55	4.0 [c]
♂	TxN3M0 IIIB	SCC	Central	7	1	58	4	Embolism	3	34	9.0 [c]
♂	T4NxM0 IIIB	SCC	Central	7	1	66	4	Embolism	3	109	18.6
♂	T4N2M0 IIIB	Adeno	Peripheral	13	1	14	0	Embolism	3	27	3.7 [c]
♀	T4NxM0 IIIB	Adeno	Central	11	2	51	0	Embolism	3	44	9.3 [c]
♂	T4N3M0 IIIB	SCC	Central [b]	12	1	50	3	Tumor abscess	3	144	31.9 [c]
♂	T4N2M0 IIIB	SCC	Central [b]	13	2	57	0	Tumor abscess	5	35	3.6 [c]
♂	T4N2M0 IIIB	SCC	Central [b]	12	1	66	3	Tumor abscess	4	91	13.0 [c]
♀	T4NxM0 IIIB	SCC	Central [b]	15	1	66	4	Tumor abscess	3	87	20.3 [c]
♂	T2N2M0 IIIA	Large-cell	Peripheral [b]	14	1	66	1	Tumor abscess	5	104	9.9 [c]
♂	T2N2M0 IIIA	SCC	Central	8	1	62	4	Lung abscess	5	102	5.5 [c]
♂	T4N2M0 IIIB	SCC	Central	10	1	60	4	Lung abscess	3	127	19.0 [c]
♂	T4N3M0 IIIB	Large-cell	Central	6	1	66	2	TO-fistula	4	74	12.7 [c]
♀	T2N2M0 IIIA	Large-cell	Central	14	2	54	0	TO-fistula	5	105	4.0 [c]
♀	T4NxM0 IIIB	Adeno	Central	11	1	46	2	Pneumonia	3	88	5.1 [c]
♂	T4NxM0 IIIB	Large-cell	Central	7	2	49	0	Pneumonia	3	68	32.8 [c]
♀	T2N2M0 IIIA	Large-cell	Central	5	1	60	5	Pneumonia	5	51	1.7 [c]

TNM, tumor-node-metastasis; WBC toxicity, leucocytopenia; SCC, squamous-cell carcinoma; Large-cell, large-cell undifferentiated carcinoma; Adeno, adenocarcinoma; CCRT, concurrent chemoradiotherapy; TO-fistula, trachea-oesophageal fistula.
[a] Cisplatin-etoposide (1) or cisplatin-docetaxel (2), [b] patients with tumor cavitation, [c] deceased.

Two remaining patients underwent (multiple) surgical intervention(s), which consisted of open-window thoracostomy and muscle transposition into the thoracic cavity. *Aspergillus fuminatus* was reported in pathological specimens derived from cavities of both patients. Despite surgical intervention, one patient died of Two remaining patients underwent (multiple) surgical intervention(s), which consisted of open-window thoracostomy and muscle transposition into postoperative complications and the other died of massive bleeding from the ipsilateral pulmonary artery 8.9 months after surgery.

The eight patients with baseline tumor cavitation, who did not develop any acute pulmonary toxicity of grade III or more, had intrathoracic disease progression within 7.3 months (*n* = 3), brain metastasis manifesting between 4.6 and 15.5 months (*n* = 3), or bone metastasis after 3.4 months (*n* = 1) as first site of recurrence. Only one patient was alive after 48.8 months without progression of disease.

Figure 1. Overall survival for patients with or without tumor cavitation. ©+, patients with cavitated tumors; ©-, patients with noncavitated tumors.



Discussion

The use of bi- and trimodality treatment strategies in patients with stage III NSCLC has increased awareness of the potential for severe treatment-related toxicity. We observed an 18% incidence of pretreatment tumor cavitation in 87 consecutive patients with stage III NSCLC at our center, with half developing acute pulmonary toxicity of grade III or more, including five patients with grade V complications. Despite a lack of consistent published data on the prognostic role of pretreatment tumor cavitation,[7–9] patients in our study cohort with cavitated tumor developed serious complications during or after CCRT.

The etiology of the observed toxicity is unclear. CCRT increases the likelihood of high-grade neutropenia; in our cohort, six of 10 patients who developed pneumonia of grade III or more and/or abscess, had experienced leucocytopenia of grade III or more. Both the tumor cavitation (in SCC) and leucocytopenia may have increased the risk of developing infectious complications. However, 48 other patients with grade III/IV leucocytopenia did not experience these problems, a group that included 20 with SCC. Of the total cohort, five patients developed an infection and/or abscess in the tumor cavity, representing 6% of all patients.

To the best of our knowledge, no previous reports have highlighted such a high incidence of complications related to tumor cavitation during or after CCRT in phase III trials or recent meta-analyses.[2–5,14] Publications of randomized clinical trials may have failed to identify some clinical toxicities, as a result of patient selection and insufficient follow-up.[15] In addition, regional differences in the incidence of squamous-cell tumors may also have contributed to under-reporting. For example, only 33% of patients in a large phase III CCRT trial from the United States had SCC,[4] whereas 43% of patients in the present study had SCC. In the Netherlands, the proportion of non-SCCs increased between the periods 1989 to 1993 and 2004 to 2009, from 42% to 67% for male patients and from 67% to 81% for female patients.[16]

Yet another explanation for the observed tumor cavitations and complications could be the relatively large primary tumor size in our patients, as 30% had a tumor measuring 8 cm or larger. A recent report suggests that many European centers consider tumors measuring more than 8 to 10 cm to be suitable for only palliative treatment.[17] Similarly, a recent European Organisation for Research and Treatment of Cancer (EORTC) study excluded patients if the tumor volume required a radiation field encompassing 12 cm or more of the esophagus in the high-dose region.[18]

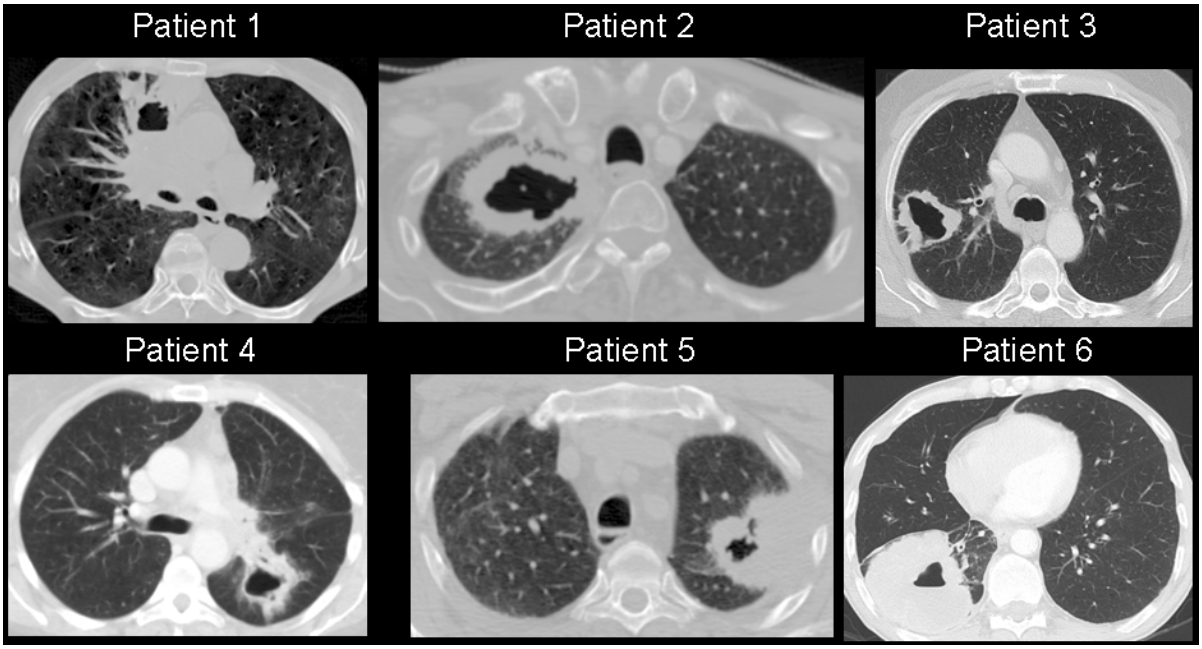
High-dose radiotherapy may contribute to tumor cavitation because of radiation-induced decreases in regional lung perfusion,[19] and central tumor necrosis has also been observed after two fractions of 18 Gy in patients undergoing stereotactic radiotherapy.[20] Although fluoro-2-deoxy-D-glucose positron emission tomography may also identify central tumor necrosis, baseline tumor cavitation identified on fluoro-2-deoxy-D-glucose positron emission tomography has not been shown to be a poor prognostic feature.[21] However, it should be pointed out that patients in the last mentioned report did not undergo CCRT.

A study of transthoracic aspirates from cavitating tumors showed that six of seven febrile patients had positive aspiration cultures at diagnosis.[22] Since 2009, cone-beam CT scans are routinely performed during the course of radiotherapy at our center, and this can potentially facilitate the earlier detection of tumor cavitation and/or abscess during CCRT. Early identification of tumor cavitation may indicate a need for treatment using appropriate antibiotics. Surgical management of lung abscess has been previously described in 247 patients, excluding abscesses secondary to carcinoma.[23] Despite conservative treatment in all, 119 and 58 patients underwent subsequent surgical drainage or pulmonary resection, respectively. Surgical drainage cured 67.2% of patients, 11.8% improved but needed additional interventions, and 21% died. Two of the patients in our report underwent open-window thoracostomy for acute complications of a tumor abscess within 5 months post-CCRT, after failure to respond to the IV administration of antibiotics. Nevertheless, one died of postoperative complications. Currently, we consider early surgical drainage when conservative treatment strategies fail.

Some limitations of the present study must be recognized, one of which is the fact that it is restricted to patients in whom all follow-up was performed within the VU University Medical Center. Although overall survival between patients with or without tumor cavitation was not significantly different in this relatively small study, our findings suggest caution when using CCRT in this setting.

We postulate that primary surgical resection with postadjuvant chemoradiotherapy in patients who are potentially resectable could be a strategy to prevent complications of tumor cavitation. In addition, administration of weekly low-dose chemotherapy is potentially a less toxic alternative. Finally, evidence of infection in a developing cavity requires aggressive antibiotic treatment and probably early surgical intervention.

Appendix 1. Pretreatment tumor cavitation in six study patients



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