

Survival After Surgical Treatment of Lung Cancer Arising in the Population Exposed to Illegal Dumping of Toxic Waste in the Land of Fires ('Terra dei Fuochi') of Southern Italy

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Abstract. *Aim: Terra dei Fuochi (TdF), the so-called 'Land of Fires' in Southern Italy, is an agricultural territory characterized by illegal dumping of toxic waste known to occur since the 1980s. It is unknown whether prognosis of patients developing cancer and living in that area may differ compared to those living in areas not exposed to this specific type of pollution. We retrospectively analyzed the 5-year survival rates of patients originating from the TdF diagnosed with lung cancer compared to patients from other areas. Materials and Methods: Patients consecutively operated on for non-small cell lung cancer (NSCLC) between November 2004 and April 2013 at the Division of Thoracic Surgery of the National Cancer Institute of Naples were eligible. The study outcome was overall survival (OS). In addition, the TdF and non-TdF groups were compared through propensity score matching (PSM). Results: Overall, 439 patients with resectable NSCLC were operated on, 123 (28%) from the TdF and 316 (72%) from other referral centers of our*

catchment area. There were 301 males and 138 females; the median age of the entire surgical population was 65 years (range=25-83) years. Apart from a different prevalence of hypertension and underweight patients, preoperative factors were evenly distributed between the two groups. At univariate analysis, OS was not different between the TdF and non TdF group (median 72 and 68 months, respectively; $p=0.75$ log-rank test). Multivariable analysis confirmed that living in the TdF area had no prognostic impact (hazard ratio=1.05; 95% confidence interval=0.70-1.57; $p=0.78$) on OS. PSM confirmed no statistically significant difference of OS (hazard ratio=1.01, 95% confidence interval=0.67-1.52; $p=0.93$). Conclusion: Following surgery for lung cancer, TdF and non-TdF surgical candidates had similar long-term survival. Originating from the TdF does not seem to be associated with worse outcomes after surgical treatment of patients with lung cancer.

A few areas in the world are so largely exposed to pollutants and contaminants due to illegal dumping of toxic waste that they can be considered potential 'open laboratories' for biomonitoring and epidemiological, genetic and translational cancer research efforts (1). One of these areas spans between the southern Italian provinces of Naples, Salerno and Caserta, affecting the population of 57 townships in the Campania Region where for decades interred or burnt toxic waste have generated dark, malodorous fumes rising from the ground of this agricultural territory, leading to its being named Terra dei Fuochi (TdF), 'Land of Fires'.

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Key Words: Lung cancer, surgery, pollution, waste dumping, Terra dei Fuochi.

Since 2004, the Triangle of Death defined by the townships of Nola, Acerra and Marigliano has been identified as the epicenter of growing public concern due to the ever increasing rates of congenital malformations and all types of cancer.

In Italy the lung cancer age-standardized incidence rates reached their peak in men during the late 1980s (94 per 100,000/year) and decreased thereafter to an estimated value of 56 per 100,000 person-years in 2015. In women, the rates increased linearly from 8 per 100,000 person-years in 1970 to 20 per 100,000 person-years in 2015. If the present mortality trends continue after 2015, lung cancer will become the most lethal cancer in females (2). In Italy, 41,500 new patients were expected to be diagnosed with lung cancer in 2015, ranking second and third among the most frequent types of cancer affecting Italian men and women, respectively. In addition, lung cancer deaths accounted for 27% of all cancer mortality in males and 11% in females, ranking first and third among all causes of mortality due to cancer in Italy (3). The most recent overall survival (OS) data after diagnosis of lung cancer in Italy are discouraging, with 5-year survival rates of 11% and 16% for men and women, respectively. In 2015, data collected from the National Institute of Health, by hospital discharge notes, showed that when the incidence of lung cancer was stratified by geographic distribution, the standardized incidence rates (SIR) per 100,000/year for the population were higher in the Northern compared to the Southern Italy (37.0 vs. 34.0) (4, 5). When the Campania region alone was analyzed, the SIR was 46.0. The same trend was also found when data were stratified by gender. Accordingly, Campania is currently deemed the Italian region at highest risk for and with the highest mortality from lung cancer (6).

In 2014, the conclusions of an epidemiological survey of the health condition of the population living in 57 townships of the TdF carried out by the Italian National Institute of Health, were published on their website (4). According to the National Institute for Statistics, as of July 2015, the overall population in the 57 TdF townships was 2,316,354 resident population out of 5,861,529 in the entire region (39.5%).

Three indicators (namely mortality, hospital admissions, and incidence of all cancer) were analyzed through the collection of data between 2003 and 2011 on the total number of deaths, the standardized mortality ratio (SMR) compared to Campania regional mortality rates adjusted by the deprivation index (DI), the total number of admissions and the standardized hospitalization ratio (SHR) compared to the Campania regional hospitalization rates adjusted by the DI, and the standardized incidence ratio (SIR) adjusted by the DI. The results of the study showed that the overall mortality in the TdF was in excess of the regional data (SMR between 104 and 110 for male and between 106 and 113 for female patients). In particular, lung cancer was amongst the

conditions for which all three indicators were estimated to be in excess of the Campania regional figures (SIR 116 and 119, SMR 111 and 110 and SHR 107 and 103 for male and female patients, respectively, in the province of Naples alone) (4). More recently, in the January 2016, the results of Sentieri project confirmed an increase of mortality and incidence of cancer pathologies specifically in the younger population of the TdF (7).

Apart from the epidemiological data from the Sentieri project, no information is currently available regarding survival after treatment of patients with lung cancer originating from the TdF who might have been exposed to by-products of illegal recycling of toxic waste. Accordingly, the purpose of this study was to provide clear information on the outcome of surgery in patients from the TdF compared to the non-TdF areas. In fact, this patient population was homogeneously approached in term of diagnostic and therapeutic pathways. The main administered treatment was solely surgery by the same surgical team. We wanted to understand whether irrespective of the possible causative link represented by the illegal waste dumping in the TdF areas, patients from the TdF would behave differently from a clinical standpoint compared to patients originating from other areas. We felt that such information could be as important for the population living in those areas as it could be for surgeons who might be faced with practicing in an area with increased lung cancer prevalence. To this purpose, we retrospectively analyzed the OS in patients originating from the TdF diagnosed with lung cancer compared to patients from other catchment areas.

Materials and Methods

To provide only standardized data and procedure, all patients consecutively operated on for non small cell lung cancer NSCLC between November 2004 and April 2013 at the Division of Thoracic Surgical Oncology of the G. Pascale National Cancer Institute, in Naples, Italy were eligible. All the patients followed the same workflow procedure with: a preoperative oncological work-up including chest x-ray, fibrotic bronchoscopy (since 2010 with the addition of endobronchial navigation to diagnose suspected mediastinal adenopathies and pulmonary nodules), computed tomographic (CT) scan of the chest and upper abdomen with contrast enhancement and total body PET scanning (after 2006). Unless symptoms indicated its need, brain CT was not routinely obtained. Video-assisted mediastinoscopy, anterior mediastinotomy and video-assisted thoracoscopic surgery were used if multiple-station mediastinal N2 disease was to be confirmed. Indeed, single-station N2 disease is currently considered a surgical subset by the institutional Tumor Board and patients are referred for adjuvant treatment within 2 months of surgery. The surgical technique included pulmonary resection performed via minithoracotomy either open or with video-assistance (*i.e.* hybrid); mediastinal nodal sampling or complete nodal dissection according to the guidelines issued by the European Society of Thoracic Surgeons was routinely performed to complete the procedure (8).

The data from the thoracic surgical patients were prospectively collected in a multivariable dataset and updated each week by one of the staff thoracic surgeons based on the in- and outpatient available information. The observation period for this study ended on May 31, 2014. The follow-up was conducted primarily through outpatient visits. Telephone and primary physician interviews were considered as an alternative only if the patients could not be followed-up through the above mentioned procedures. The last follow-up visit was the final one before 31st May 2014; no patients dropped out. The study outcome was OS, defined as the time from surgery to death from any cause. Preoperative risk assessment was conducted by categorizing surgical candidates according to the Charlson Comorbidity Index (CCI) (9). Postoperatively, complications were rated according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4 (10).

Chi-square or *t*-test were used for univariate analysis of categorical and continuous variables as indicated. The log-rank test was performed to compare survival curves. Cox regression analysis was used to assess the survival risk ratio of exposure in the TdF in the multivariate model and adjusted for propensity score, assuming a statistical significance level at $p < 0.05$. Propensity score analysis was performed by using the matching radius algorithm using calipers of width equal to 0.2 of the standard deviation of the logit of the propensity score (11). Assumption of proportional hazards was tested using the tests of the non-zero slope according to Therneau and Grambsch (12).

The entire statistical analysis was performed using STATA 14 (Stata Corp., College Station, TX, USA).

Results

Between November 2004 and April 2013, 439 patients were diagnosed and treated for clinical early-stage primary NSCLC at the Division of Thoracic Surgical Oncology of the G. Pascale National Cancer Institute in Naples, Italy. According to the list issued by the Italian Government of the 57 townships at risk from the provinces of Naples and Caserta, there were 123 patients (28%) from the TdF and 316 (72%) from other referral centers of our catchment area with resectable NSCLC (13). All the remaining areas in the Campania region not included in the TdF according to this list and the non regional referrals from other parts of southern Italy not involved in similar epidemiological contexts were included as non-TdF centers (*i.e.* the provinces of Benevento, Avellino, Salerno and some Naples townships).

Baseline characteristics of patients, grouped by residency in or not in the TdF are reported in Table I. A slightly but statistically significantly higher rate of patients with hypertension (60% *vs.* 46%, $p = 0.01$) and lower body mass index (BMI; 0% *vs.* 2%, $p = 0.04$) was found in TdF Group. On the contrary, there was no statistically significant difference in the distribution of gender, age, hemoglobin level, diabetes, arrhythmia, previous neoadjuvant chemotherapy, smoking habit, forced expiratory volume in 1 second (FEV1), diffusion lung for carbon monoxide (DLCO) and CCI.

Similarly, there was no statistically significant difference in surgical procedures, complications and side-effects of

Table I. Baseline preoperative patient characteristics of Terra dei Fuochi (TdF) and non TdF groups.

Variable	Non TdF (n=317), n (%)	TdF (n=123), n (%)	<i>p</i> -Value
Gender			0.55
Female	102 (32%)	36 (29%)	
Male	215 (68%)	87 (71%)	
Median age			0.10
≤65 Years	153 (48%)	70 (57%)	
>60 Years	164 (52%)	53 (43%)	
Median BMI			0.34
≤26.8 kg/m ²	164 (52%)	60 (49%)	
>26.8 kg/m ²	153 (48%)	63 (51%)	
Median Hb			0.10
≤13.9 g/dl	160 (51%)	60 (49%)	
>13.9 g/dl	157 (49%)	63 (51%)	
Diabetes			0.73
No	272 (72%)	104 (70%)	
Yes	45 (28%)	19 (30%)	
MI			0.18
No	301 (95%)	118 (96%)	
Yes	16 (5%)	5 (4%)	
Arrhythmia			0.98
No	304 (72%)	13 (72%)	
Yes	13 (28%)	5 (28%)	
Hypertension			0.01
No	169 (53%)	49 (40%)	
Yes	148 (47%)	74 (60%)	
Induction chemotherapy			0.42
No	292 (92%)	116 (94%)	
Yes	25 (8%)	7 (6%)	
Current smoker			0.73
No	132 (42%)	49 (40%)	
Yes	185 (58%)	74 (60%)	
Never smoker			0.42
No	289 (91%)	115 (93%)	
Yes	28 (9%)	8 (7%)	
Median FEV1			0.49
≤2.23 l	156 (49%)	65 (53%)	
>2.23 l	161 (51%)	58 (47%)	
Median DLCo*			0.09
≤84.4%	156 (52%)	52 (43%)	
>84.4%	142 (48%)	68 (57%)	
Charlson comorbidity index			0.59
0-2	216 (71%)	87 (74%)	
3-7	101 (29%)	36 (26%)	

BMI: Body mass index; Hb: hemoglobin; FEV1: forced expiratory volume at 1 second; DLCO: diffusing lung capacity for carbon dioxide. *Not available in 24 patients (19 non-TdF and 5 TdF; $p = 0.59$).

surgery, nor in clinical or pathological tumor stage and histology, between TdF and non-TdF patients (Table II).

Overall, 120 patients of the entire cohort (27%) had died at study end, with an estimated median survival time of 70 (95% CI=62-98) months. Cause of death was cancer-related in 43 patients (10% of the total; 35% of all deaths). At univariate analysis, there was no prognostic impact of residency in or

Table II. Postoperative patient characteristics of Terra dei Fuochi (TdF) and non-TdF groups.

Variable	Non TdF (n=317), n (%)	TdF (n=123), n (%)	p-Value
Type of surgery			0.97
Sublobar resection	60 (19%)	24 (20%)	
Lobectomy	201 (63%)	78 (63%)	
Pneumonectomy	56 (18%)	21 (17%)	
Postoperative complications			0.80
No	135 (43%)	54 (44%)	
Yes	182 (57%)	69 (56%)	
CTCAE v.4 grade			0.54
1	3 (1%)	3 (2%)	
2	66 (21%)	23 (19%)	
3	43 (14%)	19 (15%)	
4	15 (5%)	8 (6%)	
5	9 (3%)	1 (1%)	
Adenocarcinoma			0.58
No	140 (44%)	58 (47%)	
Yes	177 (56%)	65 (53%)	
Favorable biology **			0.73
No	279 (88%)	110 (89%)	
Yes	38 (12%)	13 (11%)	
pStage			0.81
I	230 (74%)	89 (72%)	
II	24 (8%)	13 (11%)	
IIIA	53 (17%)	20 (16%)	
IIIB	3 (1%)	1 (1%)	

cStage: Clinical stage; pStage: pathological stage; CTCAE v.4: Common Terminology Criteria for Adverse Events version 4 grade. **Adenocarcinoma *in situ*, minimally invasive adenocarcinomas and typical carcinoids.

outside of the TdF on OS ($p=0.75$; log-rank test), with median survival of 72 and 68 months, respectively (Figure 1). The median survival for patients dying from their cancer was 33 months (range=24-38 months). There was no statistically significant difference between TdF and non TdF groups as to cancer-related death [hazard ratio (HR)=1.41, 95% confidence interval (CI)=0.90-2.21; $p=0.14$].

After confirming that the assumption of proportional hazards was not violated for variables over time ($p>0.05$; tests of the non-zero slope), diabetes, hypertension, preoperative median hemoglobin level, median FEV₁, CCI, primary tumor PET standardized uptake values greater than 5, and, no history or current smoking habit showed no difference in HR of death at Cox proportional hazard analysis (Table III). Conversely, preoperative factors such as male sex, age older than 65 years, high BMI, median DLco, induction chemotherapy, adenocarcinoma histotype, favorable biology (*i.e.* adenocarcinoma *in situ*/minimally invasive adenocarcinoma and typical carcinoids), type of surgery and pathological stage were all associated with OS at Cox proportional hazard analysis, as shown in Table III.

Table III. Log-rank analysis survival prognosticators after surgical treatment of 440 patients (see text).

Variable	HR of death	95% CI	p-Value
Gender			0.0006
Male vs. female	2.00	1.40-2.85	
Median age			0.008
≤65 vs. >65 Years	1.57	1.11-2.22	
Median BMI			0.01
>26.8 vs. ≤26.8 kg/m ²	1.50	1.07-2.12	
Diabetes			0.93
No vs. yes	1.15	0.70-1.89	
Hypertension			0.21
No vs. yes	1.24	0.88-1.75	
Median Hb			0.31
>13.9 g/dl vs. ≤13.9 g/dl	1.19	0.84-1.67	
Median FEV ₁			0.12
>2.23 L vs. ≤2.23 L	1.30	0.92-1.83	
Median DLco			0.01
>84.4% vs. ≤84.4%	1.54	1.08-2.19	
Induction chemotherapy			0.0003
No vs. yes	2.41	1.18-4.91	
Never smoker			0.07
Yes vs. no	2.41	1.23-4.70	
Charlson index			0.11
≤2 vs. >2	1.33	0.91-1.95	
T factor median PET-SUV			0.22
≤5 vs. >5	1.40	0.81-2.41	
TdF			0.93
Yes vs. no	1.01	0.69-1.48	
Adenocarcinoma histotype			0.0003
Yes vs. no	1.87	1.32-2.65	
Favorable biology			0.005
Yes (AIS/MIA and carcinoid) vs. no	2.62	1.61-4.26	
Type of surgery			<0.0001
Lobar vs. sublobar	1.00	0.65-1.56	
Pneumonectomy vs. sublobar	2.50	1.40-4.47	
pStage			<0.0001
II vs. I	2.93	1.51-5.68	
IIIA vs. I	3.05	1.81-5.13	

TdF: Terra dei Fuochi; BMI: body mass index; Hb: hemoglobin; FEV₁: forced expiratory volume at 1 second; DL_{CO}: Diffusing lung capacity for carbon dioxide; AIS: adenocarcinoma *in situ*; MIA: minimally invasive adenocarcinoma; hazard ratio: hazard ratio; CI: confidence interval.

At Cox multivariate proportional hazard analysis, the lack of association of TdF origin with prognosis was confirmed (HR=1.05, 95% CI=0.70-1.57; $p=0.78$). Conversely, age, BMI, adenocarcinoma histotype, induction chemotherapy, and, pathological stage, all retained prognostic significance (Table IV).

To confirm this finding, deriving from an observational study, we used the propensity score method report measures of effect similar to those deriving from randomized experiments. All variables potentially involved in

Table IV. Cox multivariate regression analyses of survival prognosticators after surgical treatment of 440 patients.

Covariate	HR	95% CI	p-Value
Age: ≥ 65 vs. < 65 years	0.57	0.39-0.83	0.004
BMI: ≥ 26.8 vs. < 26.8 kg/m ²	0.62	0.42-0.91	0.01
Induction chemotherapy: No vs. yes	1.83	1.01-3.32	0.04
Adenocarcinoma histotype: Yes vs. no	1.56	1.02-2.37	0.03
pStage: II vs. I	2.38	1.36-4.15	0.002
pStage: IIIA vs. I	2.84	1.77-4.56	< 0.0001
TdF: Yes vs. no	1.03	0.69-1.53	0.87

BMI: Body mass index; pStage: pathological stage; TdF: Terra dei Fuochi; hazard ratio: hazard ratio; CI: confidence interval.

determining the outcome were included in a propensity score model (14).

Cox regression analysis using the propensity score yielded an HR=1.01, 95% CI=0.67-1.52, $p=0.93$ for the TdF group, confirming the previously described findings.

Discussion

Epidemiological studies on solid waste-related toxic effects can be biased by lack of reliable assessment of exposure, uncertain evaluation of the eco-systems, and missing information on relevant confounding factors. A systematic review of the literature on the reliability of epidemiological evidence on municipal solid waste disposal published in 2009 demonstrated that studies on a causal association between toxic waste in landfills and lung cancer were lacking sufficient quality, consistency and power, whereas the evidence for the relationship between lung cancer and incinerator waste disposal was considered credible but severely limited by confounders. When the relative risk of developing lung cancer was calculated for populations living within 3 km from landfills and incinerators, a value of 1.14 (95% CI=1.11-1.17) was estimated (15).

In a report from the World Health Organization on the waste management in Campania, the emphasis was placed on illegal and uncontrolled dumping since the 1980s generating an intense environmental pressure in these areas. This correlation study focused on the health effects of illegal waste dumping in 196 municipalities from the provinces of Naples and Caserta in the 1994-2001 period. At that time, the population living in that region was almost 4 million (1,921,315 men and 2,023,954 women), with an overall cancer mortality in excess of 37,000 men and 25,000 women. In the same period, lung cancer mortality comprised 12,247 men (33% of the total cancer mortality) and 2,190 women (8%). In particular, a 5.5% (95% CI=0-11.2) excess relative

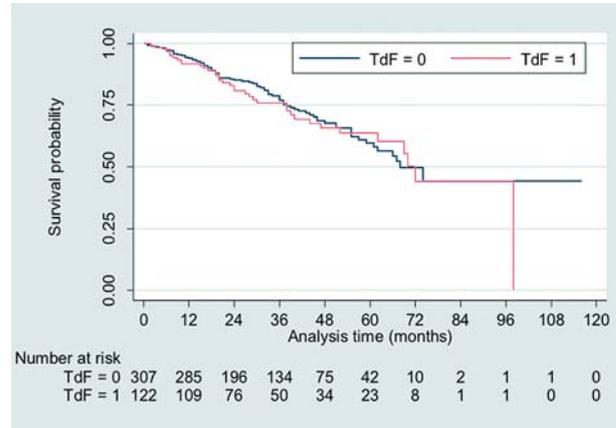


Figure 1. Kaplan–Meier survival curves for patients originating in the Terra dei Fuochi (TdF) compared to other patients from our catchment areas (see text). Hazard ratio=1.41, 95% confidence interval=0.90-2.21; $p=0.14$.

risk for lung cancer mortality was noted in men with a trend adjusted by a DI of 4.9% (95% CI=3.4-6.4) (16).

To our knowledge, this is the first report of the outcomes of treated patients with lung cancer from the TdF. However, this study has several limitations since it focused on a selected group of patients hospitalized for diagnosis and treatment; the denominator, *i.e.* the number of patients with lung cancer from the TdF receiving alternative treatments, is difficult to assess given the phenomenon of migration of southern patients to other Italian regions for the completion of care mainly due to an excessive length of waiting lists in Campania or to logistic reasons (17). In fact, the Sentieri project represents the first attempt at obtaining reliable epidemiological data to support strategic decisions on public health. However, our contribution does not help in establishing a causative link between toxic waste dumping and the onset of lung cancer. In this setting, among the products of waste combustion, 2,3,7,8-tetrachlorodibenzo-p-dioxin, simply termed dioxin, has been related to an increased incidence of lung cancer in circumstances such as after the industrial accident in 1976 at Seveso (Milan, Italy) when dioxin was vented from a malfunctioning reactor of a chemical plant. The incidence of lung cancer among the highly exposed male population did increase, with a latency of 15 years from the accidental contamination, thereby indicating the need for a prolonged follow-up strategy since exposure to dioxin may be related to lung cancer after more than 20 years (18). However, given the recent analysis of epidemiological studies (19, 20), the International Agency for Research on Cancer has defined dioxins as carcinogens causing lung cancer in humans and classified the evidence linking dioxin exposure to lung cancer as limited (21). An

interesting finding possibly linked to the exposure to dioxins in the TdF is the increased prevalence of hypertension in this group of patients, a phenomenon also observed in the exposed population in Seveso, where increased mortality from non-malignant cardiovascular diseases was described (22).

Conclusion

Despite certain obvious limitations, this study seems a first step in ascertaining whether patients from TdF are at increased risk for more aggressive lung cancer than patients from other districts of our catchment area, as the continued exposure to toxic wastes may lead us to believe. Nevertheless, results of our study show that following surgery for lung cancer, TdF and non-TdF surgical candidates had similar long-term survival rates (HR=1.41, 95% CI=0.90-2.21; $p=0.14$). Originating from the TdF does not seem to be associated with worse outcome after surgical treatment of lung cancer.

The collection of mortality data from the Campania region started in 2003 and the creation of the surgical database of the Division of Thoracic Surgery of the National Cancer Institute in 2004 make our patient data a reliable basis for outcome analysis after surgical treatment. As an example of an 'open laboratory', the Italian government is allocating resources in favor of the communities from the TdF which will be subjected to screening programs in order to facilitate detection of early-stage cancer, together with the adoption of genome-sequencing platforms to identify potentially druggable genetic abnormalities. In this setting, a genome-sequencing study based on the patients from both TdF and non-TdF areas identified in the thoracic surgical database is in progress and should be completed by the end of 2016.

Acknowledgements

Andrea Chirico and Antonio Giordano were funded by Sbarro Health Research Organization (www.shro.org) and the Commonwealth of Pennsylvania, Department of Health, Biotechnology Research Program.

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Received January 21, 2016

Revised April 6, 2016

Accepted April 11, 2016