Conflict of interest

None declared.

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Plasma DNA levels in spiral CT-detected and clinically detected lung cancer patients: A validation analysis

Keywords:
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Biomarker assessment might improve the diagnostic algorithms used for lung cancer screening with low-dose spiral computed tomography (LDSCT) [1].

In previous case–control studies of clinically detected lung cancers, we showed that high levels of free circulating plasma DNA are strongly associated with the presence of lung cancer independently of tumor stage [2,3].

However, we also recently found that in a LDSCT screening setting, the discriminatory power of plasma DNA levels for identification of lung cancer was strongly reduced, in particular for the detection of the small adenocarcinomas that are frequently found in CT-screening protocols [4]. Nevertheless, we demonstrated that a higher amount of plasma DNA at surgery was a poor prognosis indicator for survival, and might thus represent a marker for aggressive disease.

Such discrepancies could be related to specific biological features of screen-detected tumors, and potential selection of slow-growing disease.

To validate the above findings we extended our analysis to a set of 20 spiral CT-detected lung cancer patients identified during the first 3 years (13 tumors identified in prevalence round of screening and 7 tumors in incidence rounds of screening) of the Multicentric Italian randomized trial for early detection of lung cancer (MILD), launched in 2005 at Fondazione IRCCS Istituto Nazionale Tumori (Milan). For comparison, we selected 20 clinically detected NSCLC patients undergoing lung surgery during the same period of time, and 94 disease-free smoker subjects also enrolled in the MILD trial (Table 1).

The three groups were matched for gender, age, smoking habits, as well as time of blood collection, plasma separation and storage of samples that were found to impact biomarker measurement [5]. DNA extraction and quantification were done as previously described [3]. Adenocarcinoma was the most represented histotype in both patient series whereas tumor stage IA was prevalent in screen-detected lung tumors (14 cases vs. 7 cases in the clinically detected patients).

In screen-detected lung cancer patients the plasma DNA levels at surgery (median 4.2 ng/ml, IQ range 2.6–6.4) were comparable with those of disease-free subjects (4.2 ng/ml, 3.1–5.8), and the AUC–ROC value for the discriminatory power between such groups was 0.513 (95% bootstrap CI: 0.353, 0.653). In contrast, the plasma DNA levels in clinically detected lung cancers patients (16.2 ng/ml, 11.8–26.1) were remarkably higher than those of disease-free subjects, with a value of AUC–ROC of 0.942 (0.792, 0.993), a figure consistent with that previously obtained in the published series of clinically detected lung cancer patients.

Interestingly, the AUC–ROC value for discrimination between screen-detected and clinically detected lung cancer patients was 0.903 (0.738, 0.975) (stage-adjusted AUC = 0.921; 0.812, 0.989), indicating that the release of DNA in plasma in these two series was highly different. In particular plasma DNA levels tended to show high discriminatory power in stage IA (AUC = 0.919) and stage IB-II (AUC = 1), and a lower performance in stage III patients (AUC = 0.800).

These results highlight that the release of DNA in plasma is possibly related to the establishment of a relatively advanced grade of interaction between tumor and the surrounding microenvironment and provide evidence for distinct biological phenotype of CT-detected lesions.

The possibility that circulating plasma DNA could provide a fingerprint of different aggressive behavior should be further tested within screening trials in the effort to improve the clinical management of CT-detected lung cancer.

Conflict of interest

The authors have no conflict of interest to declare.

Table 1
Series characteristics and free plasma DNA distribution in the three study groups.

	Cancer patients		Disease-free subjects, *N* = 94
	Clinically detected, *N* = 20	Screen-detected, *N* = 20	
Gender			
Male	15 (75%)	15 (75%)	70 (74%)
Female	5 (25%)	5 (25%)	24 (26%)
Age (years)			
Median (IQ range)	66 (58–74)	62 (58–69)	60 (56–67)
Histology			
Adenocarcinoma	13 (65%)	12 (60%)	
Other	7 (35%)	8 (40%)	
Free plasma DNA (ng/ml)*			
Median (IQ range)	16.2 (11.8–26.1)	4.2 (2.6–6.4)	4.2 (3.1–5.8)
Stage I			
N, median (IQ range)	12, 18.0 (12.1–34.0)	16, 4.2 (2.6–6.4)	
Stage II–III			
N, median (IQ range)	8, 15.6 (10.7–22.5)	4, 4.4 (2.0–9.1)	
Storage (months)			
Median (IQ range)	18 (9–22)	16 (6–21)	16 (7–21)

* *P*-values at Wilcoxon test for comparing DNA distribution in clinically and screen-detected patients: stage I (<0.001) and stage II–III (0.051).

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