In-vivo isolation of circulating tumor cells in non-small cell lung cancer (NSCLC) patients by a medical device

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Abstract

Currently, circulating tumor cells (CTCs) are isolated in vitro from small limited volumes of blood samples. Furthermore, CTC results for NSCLC as a prognostic and stratification biomarker are scarce. The aim of the study was to assess a functionalized and structured medical wire (FSMW) for in vivo isolation of CTCs directly from the blood of NSCLC patients, and to compare it to the Cell Search method. The device was inserted in a cubital vein through a standard cannula for thirty minutes. The interaction of target CTCs with the FSMW was mediated by an antibody directed against the epithelial cell adhesion molecule (EpCAM). To confirm the CTCs binding to the wire, the immunohistochemical staining against EpCAM as well as CD45 for negative cell selection was performed. There were 72 applications of the wire in 48 stage I-IIIB NSCLC patients (12 double applications) and 12 non cancer patients. Enumeration data was available for 34 NSCLC patients and 8 non cancer patients. For 34 patients, samples were also tested in the Cell Search system. The device was well tolerated in all 72 applications without side effects. We obtained in vivo isolation of CTCs in 32 of 34 NSCLC patients (94.1 %) with a median (range) of 13 (0-300) CTCs. The sensitivity was similar for early and late stage NSCLC patients. In the non-cancer patients, no CTCs were detected (100 % specificity). In 2 of 34 samples (5.8 %), CTCs were detected by the Cell Search method. In all matched pairs, the FSMW detected the same number or more CTCs compared to the Cell Search method.

Functional Structured Medical Wire

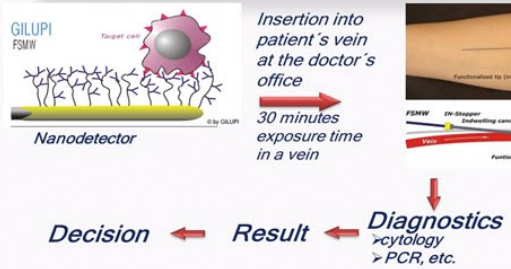
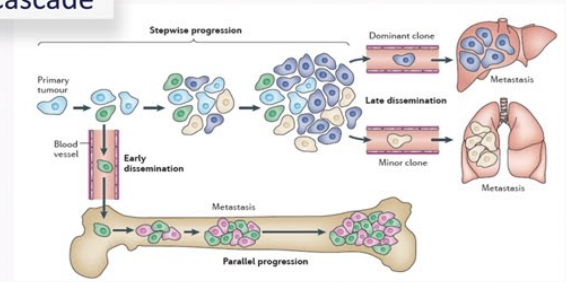


Figure 1:
The biological functionalization of the wire is achieved using an antibody against the epithelial tumor marker EpCAM. EpCAM antibodies bound to a hydrogel coating of the wire mediate specific binding of EpCAM expressing target cells.

Model of the Metastatic Cascade

Figure 4: Model of the metastatic cascade

Source: www.nature.com, A. Marusyk, V. Almendro, K. Polyak "Intra-tumour heterogeneity: a looking glass for cancer (May 2012)



Patient population

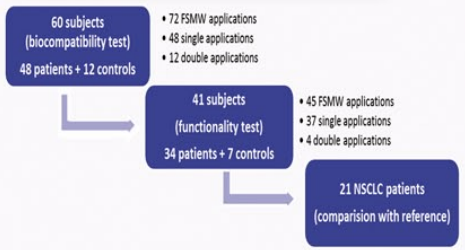


Figure 2: Design of the study.

Immunocytochemical analysis

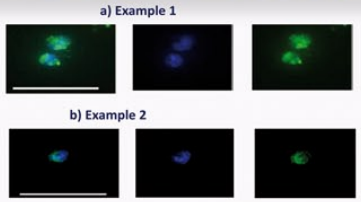
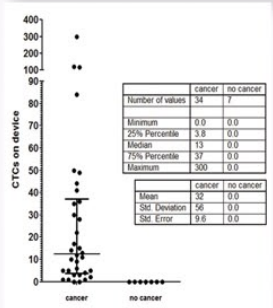


Figure 3: Immunocytochemistry analysis of CTCs captured *in vivo* with the FSMW in the blood of lung cancer patients. The CTCs were identified and enumerated via positive EpCAM and DAPI staining (respective green and blue staining in top panels), size and morphological characteristics. The white scale bar corresponds to 50µm.

Results *in vivo* captured CTCs



	cancer	no cancer
Number of values	34	7
Minimum	0.0	0.0
25% Percentile	3.8	0.0
Median	13	0.0
75% Percentile	37	0.0
Maximum	300	0.0

	cancer	no cancer
Mean	32	0.0
Std. Deviation	56	0.0
Std. Error	9.6	0.0

Figure 5:
Results of CTCs captured *in vivo* with the FSMW in the blood of NSCLC patients.

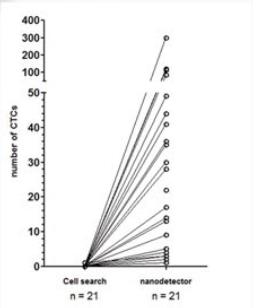


Figure 6:
Comparison of the methods, the FSMW *in vivo* and the CellSearch® method *in vitro*.

- In 100% of paired samples:

FSMW >= Cell Search

Stage	T	N	M	Total application number	Positive tested for CTC's	Detection rate (%)
IA	T1	N0	M0	3	3	100
IB	T2a	N0	M0	7	6	85,7
IIA	T2b	N0	M0	2	2	100
	T1	N1	M0	1	1	100
	T2a	N1	M0	5	5	100
IIB	T2b	N1	M0	2	2	100
	T3	N0	M0	1	1	100
IIIA	T2	N2	M0	2	2	100
	T3	N1	M0	3	2	66,6
	T3	N2	M0	1	1	100
IIIB	T4	N2	M0	2	2	100
NS	Tx	N1	M0	1	1	100
	Tx	N2	M0	2	2	100
	T2	Nx	M0	1	1	100
	N/A	N/A	N/A	1	1	100

Table 1: Distribution of the disease stages

- results from 34 subjects were included into the analysis
- CTCs could be detected in all tumor stage, including early stages

SUMMARY

- There were no AEs. All patients showed very good biocompatibility and no side effects.
- FSMW sensitivity for in vivo isolation of CTCs in NSCLC patients was **94.1 %** (32/34)
- In paired samples, only 1 patient with CTCs was detected by the CellSearch® system.
- Detection of CTC´s could be shown in **all occurred tumor stages** (especially early stages)
- The implementation of FSMW into clinical practice may improve early detection, prognosis and therapy monitoring of NSCLC patients as well as the molecular analysis of the CTCs, resulting in personalized treatment regiments

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