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Review

Carcinoembryonic antigen (CEA) as tumor marker in lung cancer

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ABSTRACT

The use of CEA as a prognostic and predictive marker in patients with lung cancer is widely debated. The aim of this review was to evaluate the results from studies made on this subject.

Using the search words "CEA", "tumor markers in lung cancer", "prognostic significance", "diagnostic significance" and "predictive significance", a search was carried out on PubMed. Exclusion criteria was articles never published in English, articles before 1981 and articles evaluating tumor markers in lung cancer not involving CEA.

Initially 217 articles were found, and 34 were left after selecting those relevant for the present study. Four of these included both Non-Small Cell Lung Cancer (NSCLC) and Small Cell Lung Cancer (SCLC) patients, and 31 dealt solely with NSCLC patients.

Regarding SCLC no studies showed that serum level of CEA was a prognostic marker for overall survival (OS).

The use of CEA serum level as a prognostic marker in NSCLC was investigated in 23 studies and the use of CEA plasma level in two. In 18 (17 serum, 1 plasma) of these studies CEA was found to be a useful prognostic marker for either OS, recurrence after surgery or/and progression free survival (PFS) in NSCLC patients. Interestingly, an overweight of low stage (stage I-II) disease and adenocarcinoma (AC) patients were observed in this group. The remaining 7 studies (6 serum, 1 plasma) contained an overweight of patients with squamous carcinoma (SQ). One study found evidence for that a tumor marker index (TMI), based on preoperative CEA and CYFRA21-1 serum levels, is useful as a prognostic marker for OS in NSCLC.

Six studies evaluated the use of CEA as a predictive marker for risk of recurrence and risk of death in NSCLC patients. Four of these studies found, that CEA was useful as a predictive marker for risk of recurrence and risk of death measured over time. No studies found CEA levels useful as a diagnostic marker for lung cancer.

With regard to NSCLC the level of CEA measured in tumor tissue in NSCLC patients, were not of prognostic, diagnostic or predictive significance for OS or recurrence after treatment.

In one study CEA level was measured in Pleural Lavage Fluid (PLF) it was here found to be useful as prognostic markers for overall survival (OS) after surgery.

In conclusion serum level of CEA carries prognostic and predictive information of risk of recurrence and of death in NSCLC independent of treatment or study design. The observation that TMI index could be a potential prognostic marker for OS in NSCLC is interesting. Future studies may benefit from evaluating more than one marker at a time, which may possibly create a more precise index for prognosis and recurrence in lung cancer, than is possible by the use of single biomarkers.

1. Introduction

Lung cancer is one of the most frequent cancer types and this combined with its very grave prognosis makes it a very deadly disease worldwide.

The incidence of lung cancer in Europe in 2008 was estimated to 390,900 cases, and 342,100 patients died of the disease [1,2], despite improvement in survival in recent years. In the quest to help patients, focus has been both on how to improve treatment, and also on selection of the best possible treatment for the individual patient. One of the issues to deal with regarding the latter problem is to be able to predict prognosis as accurately as possible, and various biomarkers have thus been evaluated for prognostic use.

The aim may be to identify patients with an extended risk of fast progression, an early recurrence after operation, when compared with other patients having same age, disease stage and other characteristics. A biomarker may be a substance that is measureable in serum or tissue, and may be of either diagnostic, prognostic or

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predictive value. Reliable prognostic tumor markers are required in order to select lung cancer patients who could benefit from for example a more aggressive treatment than the standard treatment [6]. Several potential tumor markers have been examined, with the scope of being able to identify the patients with increased risk of recurrence, short overall survival (OS) or progression free survival (PFS). One such potential marker is carcinoembryonic antigen (CEA).

CEA is a glycoprotein involved in cell adhesion, and is normally produced during fetal development but the production stops before birth. Accordingly, it is not usually present in the blood of healthy adults, CEA is a glycosyl phosphatidyl inositol (GPI)-cell surface anchored glycoprotein whose specialized sialofucosylated glycoforms serve as functional colon carcinoma L-selectin and E-selectin ligands, which may be critical to the metastatic dissemination of colon carcinoma cells [3–5]. CEA is already acknowledged and used as a tumor marker in colorectal cancer, and some have reported it to be a prognostic marker also in lung cancer. The current evidence for the latter is however questionable, and many studies have been conducted to clarify this issue. Accordingly, the aim of this review is to present an overview of all published studies evaluating CEA as a tumor marker in lung cancer, in order to clarify its role in this disease.

2. Materials and methods

Using the search words "CEA", "tumor markers in lung cancer", "prognostic significance", "diagnostic significance and predictive significance", a search was carried out on PubMed. The references in relevant articles identified were viewed for inclusion as well. Exclusion criteria was articles never published in English, articles from before 1981 and articles evaluating tumor markers in lung cancer not involving CEA.

The articles found were divided into groups according to whether they focused on NSCLC or SCLC or both. Studies where also grouped according to whether they analyzed the diagnostic, prognostic or predictive value of CEA. Also the potential role of the kind of biological material used as sample for CEA measurement was reviewed.

Statistic significance defined as a p-value < 0.05. A study was classified as "positive" if the results showed a statistic significant difference in prognosis between groups of patients with different levels of CEA. Accordingly, a study was labeled "negative" if no statistical significant difference was found.

3. Results

Among a total of 217 articles initially discovered, 34 articles fulfilled inclusion criteria. Four of these focused on both Non-Small Cell Lung Cancer (NSCLC) and Small Cell Lung Cancer (SCLC) [7–10], while 31 provided information on NSCLC.

3.1. SCLC

Four trials focused on the use of serum CEA as prognostic and predictive marker in SCLC and NSCLC. None of these four trials could be classified as positive [7–10].

Only one trial has evaluated the use of CEA as a diagnostic marker in lung cancer [14]. The authors concluded that CEA is not of any use as a diagnostic marker in neither SCLC nor NSCLC.

3.2. NSCLC: CEA expression in tumor tissue (Table 1)

The use of CEA expression in tumor tissue as a prognostic or predictive marker was evaluated in 1 trial, focusing solely on NSCLC (Table 2). CEA was not reported to be of any significant value as a tumor marker measured in tumor tissue.

3.3. NSCLC: CEA in pleural lavage fluid (Table 2)

Tomita et al. [13] evaluated the use of the level of CEA in PLF as a marker in NSCLC. The cut off value was 5 ng/ml. They observed elevated CEA level to be a significant prognostic factor for OS. (HR; 2.397; 95% CI; 0.108–0.800; $p = 0.017$).

3.4. NSCLC: evaluation of pretreatment serum CEA measurement as prognostic marker (Tables 3 and 4)

Evaluation of the suitability of serum CEA, as a prognostic marker in NSCLC, has been studied in 25 trials. Elevated CEA levels in serum were found to be a statistical significance as a prognostic marker for NSCLC in 18 of these trials (Table 3). Interestingly, the majority of patients having elevated CEA levels were of adenocarcinoma subtype. An overweight of low stage (stage I–II) cancers were observed in 12 studies, while in two studies no data were available on histology and the remaining three studies only included patients with advanced disease (stage IIIb–IV).

Arrieta et al. [11] observed high serum level of CEA to be a risk factor for development of brain metastasis and being associated

Table 1
Trials evaluating the use of CEA in tumor tissue as prognostic or predictive marker in NSCLC.

Author year	Study design, patient numbers	Parameters evaluated	Stage of disease	Histology	Treatment
Ford et al. 1981 [10]	Prospective (97 NSCLC)	CEA	NA	AC: 20 SQ: 8 LCC: 22 NOS: 55	SUR

AC, adenocarcinoma; SQ, squamous cell carcinoma; LCC, large cell carcinoma; NOS, not otherwise specified; CEA, carcinoembryonic antigen; SUR, surgery; NA, not available for evaluation.

Table 2
Trials evaluating the use of CEA in pleural lavage fluid (PLF) as prognostic and predictive marker in NSCLC.

Author year	Material	Study design, patient Numbers	Parameters evaluated	Stage of disease	Histology	Treatment	Prog. impact Y/N	Pred. impact Y/N	Early detection of progression or relapse Y/N	Other
Tomita et al. 2005 [13]	PLF	Prospective (150 NSCLC)	CEA	I: 95 II: 24 III: 31	AC: 150	SUR CTX	Y, $p = 0.017$	N	N	N

PLF, pleural lavage fluid; AC, adenocarcinoma; CEA, carcinoembryonic antigen; CTX, chemotherapy; SUR, surgery.

Table 3
Evaluation of pretreatment serum CEA measurement as prognostic marker in NSCLC with positive results.

Author year	Study design	Pts. no.	Parameters evaluated	Stage of disease	Histology	Treatment	Cut-off level	Survival	Prog. impact
Zaleska et al. [15] 2010	P	79	CEA, NSE, CYFRA21-1, ferritin, LDH, β-hCG	IIIa: 14 IIIb: 32 IV: 33	AC: 38 SQ: 26 NOS: 15	CTX	3 ng/ml	NA	$p = 0.024$
Okada et al. [16] 2003	R	265	CEA	Ia: 208 Ib: 6, II: 22 IIIa: 22 IIIb: 7	AC: 199 SQ: 62 LCC: 2 Mix: 1	SUR	5 ng/ml	5 years 49% vs 72%	$p < 0.0001$
Rubins et al. [17] 1998	P	130	CEA	I: 28, II: 7 IIIa: 12 IIIb: 28 IV: 18 US: 18	AC: 38 SQ: 39 LCC: 15 NOS: 19	SUR	3 ng/ml	3 yers AC 37% vs 48%	$p = 0.0357$
Matsuoka et al. [18] 2007	R	275	CEA CYFRA21-1	I: 275	AC: 193 SQ: 71 NOS: 11	SUR	5 ng/ml	AC: 5 years 54.6 vs 86.9%	$p = 0.0018$
Hotta et al. [19] 2000	R	39	CEA	I: 39	NA	NA	6.7 ng/ml	Median 40.2 vs 75.8 months	$p = 0.00125$
Icard et al. [20] 1994	P	152	CEA	I: 42, II: 29 IIIa: 45 IIIb: 7 IV: 2	AC: 66 SQ: 42 LCC: 2 Mix: 15	SUR	30 ng/ml	5 years 0% vs 40 stage I	$p < 0.05$
Muley et al. [21] 2004	R	153	CEA, CYFRA21-1	I: 153	AC: 75 SQ: 59 LCC: 10 Mix: 9	SUR	9.8 ng/ml	3 years 40% vs 79%	$p = 0.02$
Nisman et al. [22] 1999	P	106	TPS, CYFRA21-1, CEA.	NA	AC: 38 SQ: 43 LCC: 35	SUR	NA	RR = 5.5	$p = 0.004$
Tomita et al. [23] 2003	P	313	CEA	I: 129 II: 27 III: 89 IV: 26	AC: 220 SQ: 93	SUR	5 ng/ml	AC: 5 years 42.5% vs 77.6%	$p = 0.019$ in AC
Iwasaki et al. [24] 2004	R	70	CEA, LDH, Al-p	IV w/BM: 70	AC: 44 SQ: 21 NOS: 5	SUR	4 ng/ml	3 years 0% vs 39.6%	$p = 0.0103$.
Tomita et al. [25] 2010	R	271	TMI CEA CYFRA21-1	I: 187 II–III: 104	AC: 209 NOS: 82	SUR	5 ng/ml	5 years 48.4% vs 71.5%	$p < 0.0001$
Tomita et al. 2008 [26]	R	220	CEA	I: 78, II: 20 III–IV: 22	AC: 87 NOS: 33	SUR	2.5 ng/ml	5 years 62% vs 79.6%	$p = 0.0036$
Suzuki et al. 1999 [27]	P	365	CEA	I: 365	AC: 267 SQ: 98	SUR	5 ng/ml	5 years 48.8 vs 74.1%	$p = 0.005$ in T2
Arrieta et al. 2009 [11]	P	293	CEA.	IIIB: 29% IV: 71%	AD: 65% NOS: 35%	CTX	40 ng/ml	Mean 3.87 vs 7.8 months	$p = 0.002$
Ford et al. 1981 [10][b]	P	97	CEA	NA	AC: 20 SQ: 8 Ana: 22 NOS: 55	SUR	20 ng/ml	NA Poor prognosis	$p = 0.043$
Sawabata et al. 2002 [28]	R	297	CEA	I: 297	AC: 212 SQ: 74 LCC: 4 NOS: 7	SUR	7 ng/ml	5 years 49% vs 72%	$p = 0.00001$

Table 3 (*Continued*)

Author year	Study design	Pts. no.	Parameters evaluated	Stage of disease	Histology	Treatment	Cut-off level	Survival	Prog. impact
Kulpa et al. 2002 [29]	P[a]	200 NSCLC, 220 BLD	CYFRA21-1, NSE, CEA	I: 26, II: 25 IIIa: 34 IIIb: 98 IV: 17	SQ: 200	SUR CTX	6 ng/ml	Mean 9 vs 12 months	$p < 0.001$
Nisman et al. 1998 [30]	P[a]	94 NSCLC, 85 BLD	TPS, CYFRA21-1, CEA	I: 8, II: 16 IIIa: 8 IIIb: 16 IV: 46	AC: 41 SQ: 40 LCC: 13	SUR	4.7 ng/ml	Mean 6.8 vs 12.7 months	$p = 0.006$

BM, brain metastases; AC, adenocarcinoma; SQ, squamous cell lung cancer; LCC, large cell carcinoma; NOS, not otherwise specified; Al-p, alkaline phosphatase; LDH, lactate dehydrogenase; TMI, tumor marker index based on preoperative CEA and CYFRA21-1 levels; BLD, benign lung disease; CEA, carcinoembryonic antigen; NSE, neuro specific endolase; TPS, tissue polypeptide specific antigen; CTX, chemotherapy; SUR, surgery; P, prospective; R, retrospective; NA, not available for evaluation.

[a] Case-control study.

[b] Plasma.

with poor prognosis. Brain metastasis developed in 27 and 32% of patients at one and two years from diagnosis in patients having adenocarcinoma subtype and plasma CEA $\geq$ 40 ng/ml at diagnosis (RR 5.2; 95% CI, 1.002–29; $p = 0.05$). They suggested that surface expression of CEA on tumor cells may be a physiopathological mechanism for invasion to the CNS.

Likewise, a by Tomita et al. [25] reported CEA to be an independent prognostic factor for 5-year survival for patient having NSCLC, and suggested the use of a Tumor Marker Index (TMI), based on the preoperative serum CEA and CYFRA21-1 as a prognostic marker. Five year survival rate in patients with a TMI less than or equal to 1.0 was 72.28% compared to only 37.08% in patients with a TMI greater than 1.0 ($p < 0.0001$).

Five of the seven studies in which serum CEA levels were not found to be a significant prognostic marker for NSCLC had an overweight of non-adenocarcinoma lung cancer patients (Table 4). Three studies had majority of low stage tumors (stage I–II) and three had a majority of stage III–IV, one study did not supply data on stage of disease. Blankenburg et al. [31] did not find TMI useful as a prognostic marker for predicting prognosis in NSCLC.

3.5. NSCLC: trials evaluating the use of consecutive measurement of serum CEA during treatment and follow-up (Table 5)

Six studies evaluated whether longitudinal measurements of CEA was useful as a predictive marker or early detection

Table 4
Evaluation of pretreatment serum CEA measurement as prognostic marker in NSCLC with negative results.

Author year	Study design	Pts. no.	Parameters evaluated	Stage of disease	Histology	Treatment	Cut-off level
Blankenburg et al. 2008 [31]	R	240	CYFRA21-1, CEA TMI	I: 240	AC: 91 SQ: 100 LCC: 37 NOS: 17	SUR	6.7 ng/ml
Buccheri et al. 1993 [32]	P	360	CEA, TPA	I: 40, II: 45 IIIa: 95 IIIb: 72 IV: 108	SQ: 360	SUR	3 ng/ml
Hatzakis et al. 2002 [9]	P	84	CYFRA21-1, NSE, TPA SCC, CEA, CA-125	I-IIIa: 24 IIIb-IV: 60 .	AC: 23 SQ: 34 LCC: 24 NOS: 21	NA	20 ng/ml
Reinmut et al. 2002 [33]	P	67	CYFRA21-1, CEA	I: 43 II: 14 IIIa: 10	AC: 17 SQ: 31 LCC: 16 NOS: 3	SUR	5 ng/ml
Kobayashi et al. 2007 [34]	R	163	CEA, tumor differentiation	I: 163	AC: 136 O: 27	SUR	5 ng/ml
Schneider et al. 2003 [7][a]	P	141 NSCLC, 124 BLD	CEA, CYFRA21-1, NSE, ProGRP	I: 20, II: 6 III: 49, IV: 53 NOS: 13	AC: 39 SQ: 67 LCC: 3 Mix: 32	RTX CTX	11.2 ng/ml
Oremek et al. 2007 [8][a*]	P	59 NSCLC, 50 BLD, 80 healthy	NSE,CEA,CYFRA21-1, CRP and TNFα.	NA	AC: 29 SQ: 30	NA	4 ng/ml

AC, adenocarcinoma; SQ, squamous cell lung cancer; LCC, large cell carcinoma; NOS, not otherwise specified; BLD, benign lung disease; CEA, carcinoembryonic antigen; NSE, neuro specific endolase; ProGRP, Pro gastrin releasing peptide; TPS, tissue polypeptide specific antigen; TNFα, tumor necrosis factor alfa; RTX, radiotherapy; CTX, chemotherapy; SUR, surgery; P, prospective; R, retrospective; NA, not available for evaluation.

[a] Case-control study.

Table 5
Trials evaluating the use of consecutive measurement of serum CEA during treatment and follow-up in NSCLC.

Author year	Study design,	Pts. no.	Parameters evaluated	Stage of disease	Histology	Treatment	Cut off level	Survival	Prog. impact
Positive results									
Diez et al. 1996 [35]	P	108	CEA, CYFRA21-1, SCC	I: 55	AC: 29	SUR	5 ng/ml	AC	$p = 0.004$
				II: 12	SQ: 71			30 months 35% vs 73%	
				IIIa: 41	LCC: 8				
Kashiwabara et al. 2008 [36]	P	136	CEA	I: 136	NA	SUR	5 ng/ml	NA	$p = 0.0023$
								HR 1.650	
Buccheri et al. 2003 [37]	P	118	CEA	Ia: 27	AC: 58	SUR	10 ng/ml	NA	$p = 0.007$
				Ib: 40	SQ: 47			ROR in stage I + II 67% vs 22%	
				IIa: 5	LCC: 11				
				IIb: 12	Mixed: 2				
				IIIa: 16					
				IIIb: 15					
				IV					
Sakao et al. 2004 [38]	P	100	CEA	Ia: 36	AC: 100	SUR	5 ng/ml	NA	$p = 0.017$
				Ib: 25				ROR: 66.7% vs 23%	
				IIa: 3					
				IIb: 6					
				IIIa: 20					
				IIIb: 10					
Negative results									
Nisman et al. 1998 [30]	P	94	TPS, CYFRA21-1, CEA	I: 8	AC: 41	CTX	4.7 ng/ml	–	–
				II: 16	SQ: 40	SUR			
				IIIa: 8	LCC: 13				
				IIIb: 16					
				IV: 46					
Kao et al. 1999 [39]	P	50	CEA, CYFRA21-1	I: 20	AC: 50	SUR	NA	–	–
				II: 18					
				IIIa: 12					

AC, adenocarcinoma; SQ, squamous cell lung cancer; LCC, large cell carcinoma; NOS, not otherwise specified; CEA, carcinoembryonic antigen; TPS, tissue polypeptide specific antigen; CTX, chemotherapy; SUR, surgery; P, prospective; ROR, risk of recurrence; NA, not available for evaluation.

of progression or relapse in NSCLC. Four of these studies found observed serum CEA level increase to be significant as a predictive marker for early relapse [37], progression [38] or effect of treatment and therefore PFS [36,39]. However, two other studies [40] found no use of CEA on this matter.

4. Discussion

The histology of lung cancer has been of importance for the usefulness of CEA as a tumor marker in NSCLC. CEA has not been a useful tumor marker in SCLC patients. However in NSCLC 18 studies [8,11,15–30] reported a statistical significant evidence for the use of CEA as a prognostic marker in NSCLC patients while 7 [31–37] were negative.

CEA is most often measured in serum, though one study has examined CEA levels in PLF [13] and one study examined the expression in tumor tissue [10], respectively. The use of PLF CEA levels as prognostic markers may be promising, but should be further investigated for the occurrence of false positive. Currently, CEA measured in serum is the most convenient and examinated use of CEA as a potential prognostic biomarker in lung cancer.

The cutoff level for CEA varied among the studies between 2.5 ng/ml and 40 ng/ml. All studies except three [10,11,20] had a cutoff at 10 ng/ml or below, and the majority between 5 ng/ml and 7 ng/ml (Tables 3–5). The variations of cutoff levels are most likely due to several factors. At the low end the variation between 2.5 ng/ml and 7 ng/ml, may be due to different traditions and techniques in various geographic areas. In the three studies with cut-off values above 10 ng/ml, the results all show a significant prognostic value of serum CEA, and may possibly be the result of multiple testing, in order to find the cut-off point giving the best description of the material. The results from the majority of studies included in this review are reasonably comparable with respect to cut-off levels, when the three studies mentioned above are ruled out.

The finding of only 34 articles published through 30 years to include in this review raises a question on potential publication bias. The possibility of many negative studies never being published needs to be considered. CEA is to our knowledge is not generally used as a standard measurement in lung cancer patients, and the finding of 22 studies being positive out of 31 studies (70.97%) on CEAs prognostic value in NSCLC makes publication bias a possibility to consider. Accordingly, these data must be interpreted cautiously. CEA may carry prognostic information, but it is not in itself a sufficiently strong indicator to guide treatment decisions.

However, the use of tumor marker indexes including several tumor markers, when evaluating the patient's prognosis and risk of recurrence, might possibly be a fruitful approach in planning the treatment of lung cancer patients in the future. This is substantiated by Tomita et al.'s findings [25]; the simultaneous use of CYFRA21-1 and CEA levels may increase the power of prognostic value. Tailored treatment in advanced NSCLC is already feasible to some extend, based on histology, EGFR mutation [40], status and EML4-ALK

mutation status and this approach may be further refined in the future by the use of combinations of several biomarkers.

5. Conclusion

Serum levels of CEA may carry prognostic information in NSCLC. However the future likely lies in indexes composed of several markers and identification of mutations, which can be targets for therapy. The continuous research and development of new targeted treatment used customized to the individual patient is most needed in order to improve the grave prognosis of this disease.

Conflict of interest

None.

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