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Immunoscintigraphy Using ^{111}In -Labelled $\text{F}(\text{AB}')_2$ Fragments of Anti-carcinoembryonic Antigen (CEA) Monoclonal Antibody for Staging of Non-small Cell Lung Carcinoma

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28 patients with primitive lung cancers were imaged by immunoscintigraphy (IS) with ^{111}In indium-labelled $\text{F}(\text{ab}')_2$ anti-carcinoembryonic antigen (CEA), to assess this technique for mediastinal staging. IS revealed primitive tumours in 21 cases in whom mediastinal extension was assessed. There was concordance between clinical staging and IS confirmed by surgery in 17 cases, and discordance in 4. After surgery, discordance was in favour of IS in 2 cases (1 true positive and 1 true negative) and in favour of clinical staging in 2 (false positive of immunoscintigraphy). Anti-CEA IS could be useful for improving mediastinal staging of lung cancer.

Key words: lung cancer, staging, carcinoembryonic antigen, monoclonal antibody, radiolabel, immunoscintigraphy

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INTRODUCTION

NO MAJOR breakthroughs have recently modified the natural course of non-small cell lung carcinoma (NSCLC). The prognosis of NSCLC is directly dependent on clinical stage, thus determining the potential for surgical resection. Mediastinal lymph node involvement is a strong prognostic factor, but is difficult to assess by morphological imaging. We experimented with immunoscintigraphy (IS) as a technique for staging NSCLC.

PATIENTS AND METHODS

28 patients referred during 1991 for NSCLC were studied by IS prior to any treatment. Tumours were squamous cell carcinoma in 21 cases, adenocarcinoma in 5 cases and large cell carcinoma in 1 case. The other case, diagnosed by cytological examination as an adenocarcinoma, was shown later to have small cell lung carcinoma (SCLC) on pathology. All patients underwent a metastasis workup [1] and were classified according to the TNM classification [2]. Blood carcinoembryonic antigen (CEA) was assayed in each patient. Three days after injection of

$\text{F}(\text{ab}')_2$ fragments of anti-CEA monoclonal antibody (MAb) labelled with ^{111}In , planar images and tomographic data of the cervicothoracic region were acquired. For anatomical landmarks, images of bone structures and urinary tract, and blood pool were simultaneously acquired by injection of [$^{99\text{m}}\text{Tc}$]-methylene diphosphonate and [$^{99\text{m}}\text{Tc}$]albumin, respectively. Mediastinal involvement was finally assessed by mediastinoscopy and surgery in 14 patients, by mediastinoscopy alone in 3 patients, and in 1 patient, pleuretic involvement was proven by pleural cytology. In another patient, contralateral lung involvement was demonstrated by bronchoscopy. In the remaining 8 patients, mediastinal involvement was assessed by clinical follow-up. Endoscopic tumour samples and surgical samples were immunohistochemically stained for CEA. Anti-mouse immunoglobulin alloimmunisation was tested 8, 15 and 30 days after antibody injection.

RESULTS (Table 1)

The mean plasma CEA level was 9.2 ± 23.4 ng/ml (range 0.7–126). Immunohistochemistry (IHC) could be performed on 21 of the 28 patients and was positive for CEA in 14 cases (67%).

13 patients were considered as being free of mediastinal involvement. 15 patients were considered as having mediastinal involvement, 9 because of direct mediastinal extension (T4) and 6 because of lymph node involvement (N2 or N3).

In 7 patients, primary tumours were not detected by IS; these patients were not further investigated. In 21 patients, primary tumours were visualised with excellent contrast (Figure 1). In 17 (81%), IS was concordant with pre-operative staging, i.e. negative in the mediastinum in 6 patients who were $T \leq 3$ and $N \leq 1$, and positive in 11 patients who were T4 and/or $N \geq 2$.

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Table 1. Immunoscintigraphy results related to clinical staging, immunohistochemistry and final diagnosis

Histochemistry	CEA concentration (ng/ml)	Initial staging			Immunohistochemistry	IS results		Final diagnosis
		T	N	M		Primary tumour	Mediastinum	
AC	7.1	1	0	1	nd	—	+	Pleural puncture
AC	11.5	1	2	0	(+++)	—	—	?
AC	10.2	2	0	1	nd	—	—	?
SCC	6.1	2	0	0	(+)	—	—	Surg > pT2N0
SCC	2.1	2	0	0	(—)	—	—	Surg > pT4N0
SCC	2.6	2	2	0	(+)	—	—	Mediast > N2
SCC	2.9	3	2	0	(+)	—	+	Mediast > N2
SCC	5.5	2	0	0	(+)	+	—	Surg > pT1N0
SCC	5.3	2	0	0	(—)	+	—	Surg > pT2N1
SCC	2.9	2	0	0	(++)	+	—	Surg > pT2N0
SCC	2.1	2	0	0	(—)	+	—	Surg > pT2N0
AC	35	2	2	1	nd	+	+	?
SCC	9.8	3	0	0	(++)	+	—	Surg > pT3N1
SCC	0.7	3	0	0	(—)	+	—	Surg > pT2N0
SCC	1.7	3	2	0	(+)	+	+	Surg > pT3N2
SCC	1.6	4	0	0	(+)	+	+	Mediast > T4N0
SCC	2.3	4	2	0	(—)	+	+	Mediast > involved
SCC	1.9	4	2	0	nd	+	+	Mediast > T4N2
SCC	1.7	4	2	0	(+)	+	+	Surg > pT4N1
LCC	2	4	2	1	(—)	+	+	bronchoscopy
SCC	1.8	4	2	1	(+)	+	+	?
AC	126	4	2	1	nd	+	++	?
SCLC	3.0	4	3	0	nd	+	+	?
SCC	3.0	4	3	1	(—)	+	+	?
SCC	4.8	2	0	0	(+)	+	+	Surg > pT1N2
SCC	2.1	2	2	0	(+++)	+	—	Surg > pT2N0
SCC	1.9	2	0	0	(+)	+	+	Surg > pT1N0
SCC	2.0	4	0	1	nd	+	+	?

SCC, squamous cell carcinoma; AC, adenocarcinoma; SCLC, small cell lung carcinoma; LCC, large cell carcinoma; surg, surgical staging; Mediast., mediastinoscopy; nd, not done; IS, immunoscintigraphy.

In 11 of these 17 cases, mediastinoscopy and/or surgery confirmed the clinical and IS stage. The other 6 patients were exempted from mediastinoscopy and surgery, 4 because they had known metastases, 1 because of a lymphangitic spread in the contra-lateral lung (visualised by IS and confirmed on biopsy) and 1 because of a misdiagnosed SCLC.

In the 4 remaining patients, the IS results were discordant with clinical staging. In 2 cases, IS erroneously indicated mediastinal involvement, where these 2 patients were staged as N0. These cases both showed false positive IS results which would have led to unsuitable modification of the therapy. In the 2 other cases, IS was discordant with clinical staging, but confirmed by surgery. Taking the IS into account would have corrected the erroneous clinical stage. Indeed, 1 patient initially staged as T2 N2 M0 showed high radiolabelled antibody uptake in the primary tumour located but no mediastinal focus. The surgical staging indicated pT2 N0, confirming the absence of mediastinal involvement. In contrast, the other patient was staged as T2 N0 M0, but IS revealed a clear mediastinal focus under the aortic arch (traced by [^{99m}Tc]albumin). The surgical results revealed bulky neoplastic sub-aortic lymph nodes.

DISCUSSION

Pre-operative staging of NSCLC is of great importance. Computed tomography (CT) scanning is the best available

technique to assess mediastinal lymph node involvement, but lacks sensitivity and specificity. CT cannot depict neoplastic involvement of normal-sized lymph nodes, while all enlarged nodes are not malignant [3]. Currently, there is no consensus on the use of mediastinoscopy [2].

The assumed oncospecific aspect of IS makes it potentially attractive for enhanced staging of mediastinal lymph node involvement. IS visualises tumoral foci that are not morphologically visible, distinguishes between inflammatory and neoplastic lymph nodes, and guides peroperative biopsies. Anti-CEA is the most commonly used antibody for this application. CEA is expressed in 60–70% of NSCLC [4], as also confirmed in our study (14/21), not always resulting in a concomitant increase in circulating CEA.

Published studies [5–10] have generally focused on evaluating the feasibility of IS for lung cancer and its ability to image primary tumours and distant metastases. Few have attempted to evaluate mediastinal involvement [11] which was the objective of the present study.

In our study, visualisation of primary tumours was only a prerequisite prior to further investigation of mediastinal lesions. We evaluated the diagnostic value of anti-CEA IS for mediastinal involvement of NSCLC (N2 N3 T4).

Two problems remain in the scintigraphic imaging of the mediastinum: the limited resolution and the presence of the

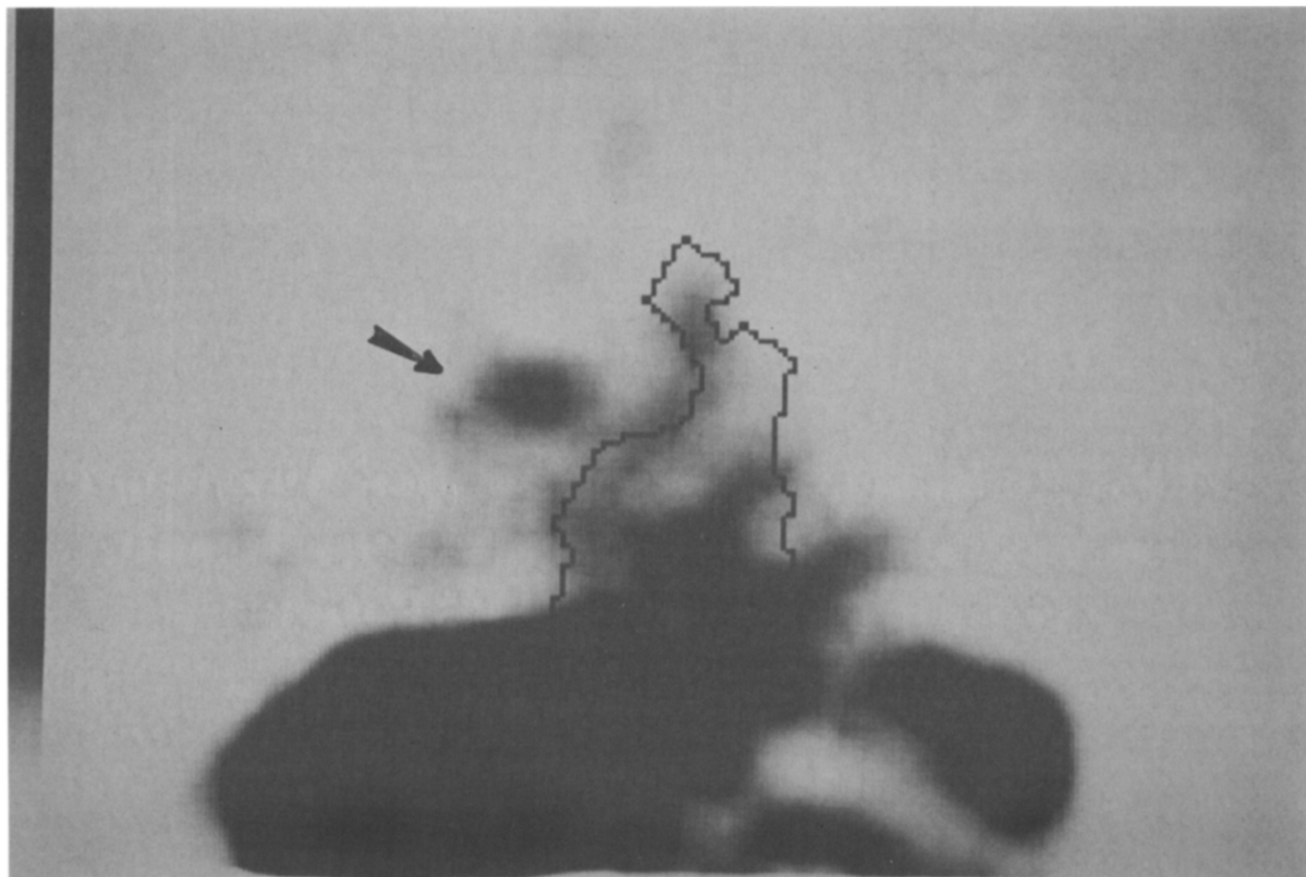


Figure 1. Patient no. 17. Frontal tomographic section. Uptake of radiolabelled anti-CEA F(ab')₂-¹¹¹In was very well defined in the right upper lobe (arrow).

heart and large vessels which can generate substantial non-specific activity. These problems can be partially overcome by using single-photon emission tomography (SPECT) and ^{99m}Tc-labelled albumin to trace vascular activity.

The determining factor before surgery is whether there is mediastinal involvement or not. We tried to determine whether IS results would modify staging of patients and, if so, to what extent and relevance (confirmed by surgical results).

In 17 patients, IS only confirmed the presence (11 cases) or absence (6 cases) of mediastinal involvement. However, data provided by the IS (presence of CEA) actually complemented the morphological data. IS increased the predictive value of staging. These 17 patients were finally correctly staged (the IS and clinical staging were never both wrong at once). Only 4 patients were reclassified. It was justified in 2 cases but not in the others. Thus, IS is definitely useful but the results must always be complemented with other analyses. When the IS results are concordant with the initial clinical staging, there is a very low probability of error and mediastinoscopy can thus be excluded. If the patient is classified as T < 4 and N < 2 and no mediastinal foci are detected in the IS, operability can be diagnosed. Conversely, when there is mediastinal involvement (T4 and/or N ≥ 2) confirmed by an IS focus, then surgery can be exempted without any further mediastinoscopic study. However, mediastinoscopy should be proposed in case of a discordance between the initial clinical staging and the IS results, since we noted that this can just as well falsely disprove a correct evaluation as correct an erroneous stage. These results could be

further improved by using new generations of tracers, such as bispecific immunoconjugates [12].

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Total Rectal Resection and Colo-anal Anastomosis for Low Rectal Tumours: Comparative Results in a Group of Young and Old Patients

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Rectal cancer incidence is increasing among the elderly who are more often considered for palliation rather than for surgical cure. Moreover, sphincter-sparing surgery is often avoided when treating the elderly. We report our experience on a consecutive series of 38 subjects, suffering from a lower third rectal tumour with a median distance of 5.6 cm from the anal verge (7 Dukes' A, 6 Dukes' B, 17 Dukes' C, 3 Dukes' D, 3 anastomotic recurrences and 2 large villous adenomas). All subjects were prospectively collected in a 2-year period and treated with total resection and colo-anal hand-sewn anastomosis on a J colic reservoir. 20 patients younger than 65 years and 18 over 65 years were matched for surgical complications, late morbidity, oncological and functional results but no statistical difference was found. Our hope is that a conservative approach in treating the low rectal tumours will progressively be accepted for elderly patients.

Key words: rectal neoplasm, colo-anal, conservative surgery, J pouch, surgery in elderly, quality of life

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INTRODUCTION

RECTAL CANCER is becoming a major public health problem in western countries where the incidence of the disease is increasing, especially among the elderly [1].

Notwithstanding the improvement of the quality and number of intensive care units, elderly patients are still more likely to be submitted to local palliation rather than radical surgical cure. Moreover, Miles's abdominoperineal amputation is still more easily conducted in the elderly than sphincter-sparing operations, adding the disability of a definitive colostomy to the already uneasy social condition of the aged. We have reviewed

our consecutive series of patients affected by lower third rectal cancer to understand the feasibility, operative risk and oncological adequacy of a hand-sewn colo-anal anastomosis, and to compare the results in a group of young versus old patients.

PATIENTS AND METHODS

38 consecutive patients, 23 males and 15 females, were seen and treated for distal rectal cancer at the Division of Surgical Oncology B, National Cancer Institute of Milan, Italy from March 1990 to August 1992. All patients had a lower tumour margin between 8 and 4 cm (median 5.6) from anal verge, and were eligible to enter the study (Table 1). 20 patients were younger than 65 years and 18 were older.

The median pre-operative Karnofsky performance status (PS) [2] was 90 (range 80–100) and, concerning elderly patients, quality of life was also investigated with the QL-Index (QL-I) proposed by Spitzer [3] (median 9, range 8–10).

7 patients had Dukes' A adenocarcinomas, 6 Dukes' B, 17 Dukes' C and 3 Dukes' D affected by synchronous liver metastases (2 patients) or lung metastases (1 patient); 3 had anastomotic recurrences after anterior resection previously per-

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