Radiolocalization of Squamous Lung Carcinoma with $^{131}$I-labeled Epidermal Growth Factor

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INTRODUCTION

NSCLCs$^3$ constitute more than 70% of all lung cancers in Western countries and represent a major cause of cancer death (1). Although several histological varieties are recognized (i.e., squamous carcinoma, adenocarcinoma, and large cell carcinoma), their clinical outcomes are similar (1). Surgery is the only curative treatment available; unresectable tumors are often treated with radiotherapy or chemotherapy, but overall survival is less than 10% at 3 years, with a median survival less than 1 year (2).

Although multimodal therapies have led to considerable progress (3), the development of novel strategies for the management of these tumors remains a priority. The recognition of the molecular abnormalities that participate in their development and/or progression provide new opportunities for improved diagnosis and/or therapy. Mutations in the c-K-ras gene seem to be indicators of poor prognosis in adenocarcinomas (4), and 10–30-fold overexpression of the EGFr occurs in most NSCLC, particularly in the squamous variety (5, 6). Up-regulated EGFr expression has been demonstrated in a wide range of human tumors, including lung cancer, breast cancer, colorectal cancer, kidney cancer, and astrocytoma, through a variety of mechanisms: (a) gene amplification, as demonstrated in A431 vulvar carcinoma cells (7); (b) gene rearrangement, as observed in some astrocytomas (8); and (c) overexpression in the absence of structural abnormalities. The latter seems to be the most common mechanism and has been reported in many types of human cancer (9). The EGFr is a transmembrane glycoprotein of $M_0$ 170,000, which contains an extracellular EGFr-binding domain, a transmembrane domain, and a cytoplasmic domain, which has tyrosine kinase activity and undergoes autophosphorylation on ligand binding (10).

Although EGFr was the first ligand recognized for the EGFr, other molecules with binding activity have been identified more recently: transforming growth factor-α, amphiregulin, and cripto (11). EGFr and transforming growth factor-α show the highest binding affinity and have been proposed to act as autocrine growth factors that may contribute to the progression of several types of cancer, including NSCLC (12). On the basis of these findings, mAbs, which block EGFr kinase activation and disrupt the autocrine loop, have been developed (13). Preliminary clinical studies have shown that $^{111}$In-labeled mAb 225 and $^{131}$I-labeled mAb 528 can localize to squamous lung carcinomas (14, 15). These studies also confirmed that a whole antibody is disadvantageous because of its large size. Furthermore, mAb RG 83852 localizes to lung and head and neck cancers and up-regulates EGFr tyrosine kinase activity (16).

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3 The abbreviations used are: NSCLC, non-small cell lung carcinoma; EGFr, epidermal growth factor receptor; mAb, monoclonal antibody; HSA, human serum albumin; AOI, area of interest.

1 The abbreviations used are: NSCLC, non-small cell lung carcinoma; EGFr, epidermal growth factor receptor; mAb, monoclonal antibody; HSA, human serum albumin; AOI, area of interest.
Because EGF, the natural EGF receptor ligand, has higher affinity than the available mAbs and a lower molecular weight (Mr 6200), we and others have initiated studies to evaluate its ability to localize to squamous cancers in an effort to improve current diagnostic tests. Schatten et al. (17) have described preliminary data suggesting that labeled EGF may be of use in the staging of patients with cervix cancer using lymphoscintigraphy. In this study, labeled EGF was administered i.v. over 4 h, because it was expected that this growth factor would be eliminated rapidly in the urine, and a prolonged infusion would allow more persistent exposure of the tumor to the EGF. Our findings indicate that recombinant EGF administered i.v. can localize to NSCLC efficiently, can be administered safely to patients, and has more favorable pharmacokinetic properties than mAbs. On the basis of these results, further studies are warranted to examine the potential of EGF or EGF-related peptides in the imaging and/or therapy of EGFR-overexpressing human cancers.

**PATIENTS AND METHODS**

**Patient Selection.** Patients (n = 9) with unresectable primary or metastatic squamous carcinoma of the lung were entered in this Phase I study, because EGF is expressed at high levels in 100% of these tumors (6); their clinical characteristics are summarized in Table 1. All patients were male; the mean age was 66 (range, 51–80) years. Eligibility criteria included a lack of curative therapy, Karnofsky performance status of ≥70, serum creatinine <1.5 mg/ml, total bilirubin <2 mg/100 ml, hemoglobin >10 g/100 ml, WBC count >4,000/μl, and platelet count >100,000/μl. Patients with serious cardiac disease (New York Heart Association class III or IV), infections requiring antibiotic treatment, other disabling diseases, pregnancy, or lactation were excluded. All patients had histologically or cytologically documented squamous carcinoma of the lung. Two patients had received radiation therapy, two had prior surgery, four had prior chemotherapy, and three had not received any prior treatment. No antitumor therapy had been administered within the 4 weeks preceding EGF administration. The trial was approved by the Ethics Committee of Hospital del Mar and by the Dirección General de Farmacia y Medicamentos (Ministerio de Sanidad, Madrid, Spain). Written informed consent was obtained from all patients.

**Radioiodination of EGF.** All materials used were sterile and pyrogen free. EGF (0.3 mg; Boehringer Mannheim, Mannheim, Germany) was labeled with 370–444 megabecquerels [131I]Na (Ire-Medgenix, Brussels, Belgium) using the chloramine T method (0.57 mg/ml; Ref. 18). The labeled product was obtained from free NaI using a sterile polyacrylamide gel column (Econo-Pac 10 DG desalting column; Bio-Rad, Richmond, CA). Preclinical quality control data showed that 30 to 39% (35 ± 3) of the labeled EGF retained binding activity, as determined by absorption assays using ASPC-1 pancreas cancer cells, under conditions of receptor excess. Assays were performed as described elsewhere with minor modifications (19). The specificity of the absorption assays was demonstrated using unlabeled EGF to displace the radiolabeled ligand. Prior experiments from our laboratory have shown that peptides unrelated to EGF do not displace binding in these assays.

**Administration of 131I-labeled EGF.** 131I-labeled EGF was administered i.v. in 154 mm NaCl containing 5% HSA (total volume, 250 ml) through a 0.22-μm Millex-GV filter (Millipore, Molsheim, France) over a 4-h period. Three patients were entered at each of the three dose level groups designed. The first group (group I) received 0.3 mg 131I-labeled EGF only; the second and third groups (groups II and III) received an additional 0.7 or 2.7 mg inconfused unlabeled EGF, respectively. The 131I-labeled EGF activity administered to patients ranged from 191 to 360 megabecquerels.

**Patient Monitoring.** Patients’ vital signs and symptoms were monitored frequently during, and up to 2 h after, EGF infusion daily for 3 days and 1 and 4 weeks after EGF administration. Complete blood counts and biochemical screening were obtained before and 7 and 30 days after the infusion. Chest X-rays and computed tomographic scans were obtained within 2 weeks of entry in the study, and chest-X-rays were repeated 4 weeks after EGF administration.

**Imaging Studies.** Anterior and posterior whole-body and spot analogue images were obtained daily in all patients, starting 3 h after completion of 131I-labeled EGF infusion and up to at least 50 h after infusion, using a gamma camera (Siemens...
Fig. 1 Chest X-ray (A), chest computed tomogram (B), and anterior chest $^{131}$I-labeled EGF (C) and $^{99m}$Tc-labeled HSA (D) scintigrams corresponding to patient 4. A large cavitated mass is present in the right upper lobe as seen in A and B. A positive tumor scan is shown 50 h after infusion of labeled EGF (arrows). The area identified in the EGF scan does not show enhanced uptake of $^{99m}$Tc-labeled HSA, ruling out nonspecific EGF tumor localization. The hot area at the top of C corresponds to the thyroid.

AOIs were drawn over the tumor, lungs, liver, heart, kidneys, and thyroid gland on the anterior and posterior digital images. To subtract the background activity of overlying tissues, AOIs were also drawn adjacent to the tumor, kidneys, and thyroid gland. Tumor:normal lung, tumor:heart, and tumor:liver uptake ratios were obtained at various time points from normalized AOIs on anterior and posterior digital images. The daily percentage of injected dose per organ was calculated by multiplying the fraction of image counts in the organ by the percentage of radioactivity in the whole body on that day. The percentage of radioactivity retention in the tumors and normal tissues during the course of the study was calculated from these data.

In patients with positive tumor images, $^{99m}$Tc-labeled HSA scans of the anterior and posterior chest were obtained on the last day of the study to rule out nonspecific $^{131}$I-labeled EGF uptake due to blood pool radioactivity.

Scintigrams were considered positive when persistent $^{131}$I-labeled EGF uptake was observed on analogue images.

Pharmacokinetic Analysis. To estimate serum radioactivity, blood samples were drawn at 0, 30, 120, and 240 min during the infusion, 1, 5, 15, 30, 60, 120, and 240 min after the end of the infusion, and twice daily thereafter for a minimum period of 3 days. To calculate the serum radioactivity $t_{1/2}$ (distribution and $t_{1/2}$ elimination), mean residence time, clearance, and volume of distribution at steady state, the PKCALC software was used (20). Twenty-four h urine was collected for estimation of urinary excretion of radioactivity during the 3 days following $^{131}$I-labeled EGF administration.

Statistical Analysis. Statistical analysis of the data was performed using the one-tailed Student’s $t$ test.
RESULTS

Imaging Studies with \(^{131}\)I-labeled EGF. In six patients, all known tumor sites showed positive tumor scans; the three other patients had negative tumor scans (Table 1 and Figs. 1 and 2). Two of the patients with negative scans corresponded to group I (patients 1 and 2), and one corresponded to group III (patient 9). In patient 9, an area of slightly increased radioactivity, corresponding to the region where the tumor was documented using X-rays, was seen on day 3 in the digital-subtracted images but not in the analogue images. To ascertain the optimal time for patient imaging, anterior and posterior analogue spot images were obtained daily in all patients up to at least 50 h after infusion; in three patients, images were obtained up to 74 h. Although the relatively long \(t_{1/2}\) of \(^{131}\)I (8 days) allows further image acquisition, it was not practical to obtain images later than 3 days due to the small amount of radioactivity remaining in the patients at that time. The best contrast between tumor and surrounding tissue was obtained in the analogue and digital spot images performed 50 or 74 h after infusion. Background subtraction performed on digital spot images improved the visualization of tumor uptake remarkably.

To determine the specificity of the tumor images observed, \(^{99}\)mTc-labeled HSA scans were obtained on the last day of the study. No accumulation of this tracer at tumor sites could be demonstrated in any of the patients studied (Table 1 and Fig. 1).

Cardiac blood pool radioactivity was observed in all patients (Figs. 1 and 2). Thyroid and gastrointestinal images of variable intensity (Figs. 1 and 2) were also observed despite
Fig. 3  Total body radioactivity clearance for each patient group. At 50 h, retention is greater at the 3-mg dose than at 1 mg ($P = 0.059$) or 0.3 mg ($P = 0.038$). Error bars (SE) are shown for the 50-h time point.

Fig. 4  Radioactivity retention in tumor (■), normal lung (+), liver (*), and serum (⊙) during the course of the study. Tumor retention is significantly higher than normal tissue retention (at 50 h, $P = 0.012$, 0.010, and 0.002 for normal lung, liver, and serum, respectively). Error bars (SE) are shown for the 50-h time point.

Table 2  Tumor:normal lung tissue uptake of $^{131}$I-labeled EGF

<table>
<thead>
<tr>
<th>Day</th>
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<th>2</th>
<th>3</th>
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</tr>
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<tbody>
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<td>3</td>
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</tr>
<tr>
<td>4</td>
<td>1.22</td>
<td>1.24</td>
<td>1.31</td>
<td>N.A.$^a$</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1.27</td>
<td>1.18</td>
<td>1.29</td>
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</tr>
<tr>
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<td>1.10</td>
<td>1.09</td>
<td>1.18</td>
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<tr>
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<td>1.26</td>
<td>1.44</td>
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</tr>
<tr>
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<td>1.53</td>
<td>1.58</td>
<td>1.72</td>
<td>N.A.</td>
<td></td>
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</tbody>
</table>

Mean ± SD: 1.28 ± 0.15$^b$; 1.30 ± 0.18; 1.35 ± 0.19$^b$; 1.39 ± 0.04$^b$

$^a$ N.A., not available.

Tumor:normal lung uptake was significantly higher at day 3 compared with day 1 ($P = 0.029$, Student’s $t$ test).

Tumor:normal tissue uptake ratios in patients with positive scans are shown in Table 2. Tumor:normal lung and tumor:heart ratios increased from day 1 to day 3 of the study ($P = 0.029$ and 0.006, respectively).

Pharmacokinetic Studies. The results of the pharmacokinetic studies are shown in Table 3. The postinfusion serum radioactivity-versus-time profile for each of the 3 dose level groups was described best by a two-compartment pharmacokinetic model (except for data from patients 4 and 7, which fitted a one-compartment model better), with $r > 0.975$ in each individual case studied. Despite the few patients included at each dose level, there was a trend of increased mean elimination $t_1/2$ and mean residence time in patients who received higher EGF doses. Clearance and volume of distribution showed a tendency to decrease at higher dose levels.

Cumulative urine radioactivity and whole-body counts accounted for >94% of the total injected dose in 4 patients with reliable urine collections, suggesting that most labeled EGF is eliminated by this route.

Adverse Effects and Clinical Observations. All patients presented adverse effects during, and a few h after, EGF infusion. Adverse reactions are summarized in Table 4. The most common symptoms were nausea, vomiting, and diarrhea. Fever and chills were frequent in patients in groups II and III; hypotension (>20-mm Hg drop in systolic pressure) was seen in group III patients. All symptoms developed during the course of the infusion. Adverse effects were more frequent and severe in patients who received the highest dose of EGF. All adverse effects disappeared a few h after the EGF infusion was terminated, with or without symptomatic treatment. Metoclopramide was used for nausea, paracetamol was used for fever, and i.v. fluids were administered when hypotension developed. There were no significant changes in any of the hematological or biochemical parameters examined during the 30 days following EGF infusion. If labeled EGF were to be used as a diagnostic reagent, 3 mg would be the maximum acceptable dose for the administration route used in this clinical trial.

In seven patients, no changes in the sizes of the tumors with positive scans, radioactivity retention at 50 h was greater in tumors than in normal tissues ($P = 0.002$, 0.010, and 0.012 for serum, normal liver, and normal lung, respectively). Kidney and thyroid radioactivity increased throughout the study, most likely as a result of iodine excretion and uptake, respectively.

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 attempts to prevent thyroid uptake of free $^{131}$I with Lugol’s solution. Weak splenic and hepatic activities were seen less frequently. There were no false-positive scans with $^{131}$I-labeled EGF.

Total body clearance of radioactivity is plotted for each EGF dose level in Fig. 3. Patient 3 has been excluded from this analysis on the basis of an abnormal renal function (serum creatinine, 1.4 mg/ml; creatinine clearance, 26 ml/min). Despite the small number of patients entered at each dose level, a significant raise of radioactivity retention was observed with increasing EGF doses ($P < 0.05$ between groups I and III at 3, 26, and 50 h).

The percentage of radioactivity retention in tumors and normal tissues during the course of the study is plotted in Fig. 4. Lungs, heart, liver, and serum radioactivity (measured in a gamma well counter) showed a similar decay rate. In patients

\(\text{Tumor: normal lung tissue uptake of }^{131}\text{I-labeled EGF}\
\|
\begin{array}{cccc}
\text{Day} & \text{Patient} & 1 & 2 & 3 & 4 \\
3 & 1.35 & 1.41 & 1.34 & 1.36 \\
4 & 1.22 & 1.24 & 1.31 & N.A.$^a$ \\
5 & 1.27 & 1.18 & 1.29 & 1.37 \\
6 & 1.10 & 1.09 & 1.18 & N.A. \\
7 & 1.21 & 1.27 & 1.26 & 1.44 \\
8 & 1.53 & 1.58 & 1.72 & N.A. \\
\end{array}
\)

Mean ± SD: 1.28 ± 0.15$^b$; 1.30 ± 0.18; 1.35 ± 0.19$^b$; 1.39 ± 0.04$^b$

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DISCUSSION

Overexpression of EGFr in NSCLC, and particularly in its squamous variety, has stimulated the development of EGFr-based diagnostic and therapeutic strategies (14–17, 21, 22). Whole-antibody molecules are disadvantageous because of their large size, which leads to greater retention and blood background levels, greater radiation exposure of normal tissues, and higher immunogenicity (23–25). In contrast, F(ab’)_2 and Fab fragments have more favorable pharmacokinetic behavior but lower affinity (26–28).

EGF, the natural EGFr ligand, has a higher affinity than the available anti-EGFr mAbs and a much lower molecular weight, and it represents an alternative strategy for in vivo imaging of human tumors that overexpress EGFr.

The present study is the first attempt to localize human tumors using labeled EGF administered by the i.v. route. It was designed on the basis of information from a prior clinical trial with anti-EGFr mAb 225, which indicated that antibody doses <20 mg (~1.33 x 10^{-7} mol) were ineffective in tumor localization (14). Therefore, the first dose administered in this study is equimolar to the first dose that yielded positive tumor localization (14). Following the observation that the cold antibody may improve the radiolocalization of the labeled antibody (14), possibly due to plasma or normal tissue saturation, we administered a fixed dose of ~31I-labeled EGF (0.3 mg, ~5 x 10^{-8} mol) and increasing doses of cold EGF (up to 5 x 10^{-7} mol). Our findings indicate that EGF doses <1.66 x 10^{-7} mol also may be ineffective in tumor localization. These data need to be confirmed in a larger patient series.

The most important observation made was that ~31I-labeled EGF can localize to squamous NSCLC. Despite the small number of patients studied, several conclusions can be drawn: (a) there was a relationship between tumor uptake and whole-body EGF retention; (b) tumors were generally detectable in the first day of the study, although uptake ratios were slightly higher at later time points; and (c) tumor uptake could not be explained on the basis of blood flow, because ~99mTc-labeled HSA failed to localize to tumors. The importance of whole-body EGF retention is substantiated by the imaging and pharmacokinetic data from patient 3. Although this patient had a normal serum creatinine level, the creatinine clearance was markedly diminished, and radioactivity retention was similar to that observed in patients who received higher EGF doses (not shown). The fact that patients who received higher doses of EGF yielded positive scans more frequently may be explained by the saturation of the normal tissue EGFr compartment. Similar findings were made when using a mAb detecting the EGFr at equimolar doses. Furthermore, the increased mean residence time of ~31I-labeled EGF in tumors also may contribute to the greater efficacy of high EGF doses. These observations should help in designing future clinical studies. The clinical trials with anti-EGFr mAbs reported until now (14–16) substantiate the importance of the dose in achieving tumor localization through EGFr binding. In these studies, a relationship between antibody dose and whole-body retention was also demonstrated.

All patients presented dose-related side effects during or shortly after the infusion of EGF. All adverse effects were self-limited, although symptomatic treatment was administered to patients receiving higher EGF doses. Although it is well known that EGF can affect intestinal epithelial cell proliferation and function (29, 30), an obvious explanation accounting for the gastrointestinal and nongastrointestinal side effects observed is not available. The combination of hypotension, nausea, vomiting, and diarrhea is reminiscent of the symptoms of carcinoid tumors, although no cutaneous flush was observed in our patients. This area will deserve further investigation. Our findings contrast with a report in which ~31I-labeled EGF was administered s.c. to patients with cervix carcinoma and no side effects were observed at the dose used (50 μg; Ref. 17). This discrepancy may be related to the higher dose used in our study or to differences in the route of administration or in the EGF preparation used. Most importantly, the lack of unexpected tumor progression in our patients suggests that at the doses used, EGF does not stimulate tumor growth.

The early tumor localization observed with EGF as compared with the labeled anti-EGFr antibody may be due to the more rapid renal excretion, greater extravascular diffusion and tumor binding, and more efficient internalization by tumor cells (31). In this regard, EGF shows clear diagnostic advantages over antibodies and is more comparable to smaller peptides, such as the somatostatin analogue Tyr-3-octreotide, which has been

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Table 3  Pharmacokinetic parameters of ~31I-labeled EGF

<table>
<thead>
<tr>
<th>Group</th>
<th>Distribution t_{1/2} (h)</th>
<th>Elimination t_{1/2} (h)</th>
<th>Mean residence time (h)</th>
<th>Clearance (litters/h)</th>
<th>Steady-state distribution volume (litters)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0.84 ± 0.40^a</td>
<td>15.2 ± 1.4</td>
<td>20.0 ± 2.0</td>
<td>1.19 ± 0.10</td>
<td>23.8 ± 4.4</td>
</tr>
<tr>
<td>II</td>
<td>0.43 ± 0.02</td>
<td>17.1 ± 4.4</td>
<td>23.9 ± 6.7</td>
<td>0.62 ± 0.16</td>
<td>14.2 ± 1.7</td>
</tr>
<tr>
<td>III</td>
<td>0.36 ± 0.23</td>
<td>24.4 ± 5.7</td>
<td>34.1 ± 7.9</td>
<td>0.49 ± 0.09</td>
<td>16.9 ± 2.5</td>
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^a Mean ± SD.

Table 4  Toxicity observed in patients receiving ~31I-labeled EGF

<table>
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<th>Side Effect</th>
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<th>Group II</th>
<th>Group III</th>
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<tr>
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<td>2/3</td>
</tr>
<tr>
<td>Nausea, vomiting</td>
<td>2/3</td>
<td>3/3</td>
<td>2/3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2/3</td>
<td>2/3</td>
<td>2/3</td>
</tr>
<tr>
<td>Headache</td>
<td>1/3</td>
<td>0/3</td>
<td>0/3</td>
</tr>
<tr>
<td>Fever, chills</td>
<td>0/3</td>
<td>2/3</td>
<td>3/3</td>
</tr>
<tr>
<td>Hypotension</td>
<td>0/3</td>
<td>0/3</td>
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</tr>
</tbody>
</table>

Table 4 shows the toxicity observed in patients receiving ~31I-labeled EGF. The most important observation made was that ~31I-labeled EGF can localize to squamous NSCLC. Despite the small number of patients studied, several conclusions can be drawn: (a) there was a relationship between tumor uptake and whole-body EGF retention; (b) tumors were generally detectable in the first day of the study, although uptake ratios were slightly higher at later time points; and (c) tumor uptake could not be explained on the basis of blood flow, because ~99mTc-labeled HSA failed to localize to tumors. The importance of whole-body EGF retention is substantiated by the imaging and pharmacokinetic data from patient 3. Although this patient had a normal serum creatinine level, the creatinine clearance was markedly diminished, and radioactivity retention was similar to that observed in patients who received higher EGF doses (not shown). The fact that patients who received higher doses of EGF yielded positive scans more frequently may be explained by the saturation of the normal tissue EGFr compartment. Similar findings were made when using a mAb detecting the EGFr at equimolar doses. Furthermore, the increased mean residence time of ~31I-labeled EGF in tumors also may contribute to the greater efficacy of high EGF doses. These observations should help in designing future clinical studies. The clinical trials with anti-EGFr mAbs reported until now (14–16) substantiate the importance of the dose in achieving tumor localization through EGFr binding. In these studies, a relationship between antibody dose and whole-body retention was also demonstrated.

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The early tumor localization observed with EGF as compared with the labeled anti-EGFr antibody may be due to the more rapid renal excretion, greater extravascular diffusion and tumor binding, and more efficient internalization by tumor cells (31). In this regard, EGF shows clear diagnostic advantages over antibodies and is more comparable to smaller peptides, such as the somatostatin analogue Tyr-3-octreotide, which has been
used for the radiolocalization of neuroendocrine tumors (32), vasoactive intestinal peptide (33), or Fv fragments.

Based on the results reported here and on other data from the literature, future clinical studies should attempt: (a) to improve EGF-labeling methods, either by optimizing the use of $^{131}$I or by using isotopes with shorter half-lives, which also have better imaging properties and deliver lower radiation doses (i.e., $^{125}$I and $^{99m}$Tc); in this sense, our attempts to improve EGF labeling and biological activity using lower doses of chloramine T and sodium metabisulfite or using the iodogen method have proven largely unsuccessful; (b) to determine the optimal dose and administration scheme (i.e., bolus versus slow infusion); (c) to improve EGF delivery to the tumor, possibly by pretargeting normal tissues with cold EGF or anti-EGF receptor antibody fragments; (d) to decrease toxicity; regarding this point, further work is necessary to establish the physiological basis for the observed side effects and to provide hypotheses for pharmacological intervention; and (e) to define the patient population that may benefit from this strategy. Although our study was restricted to patients with squamous lung cancer, other EGF receptor-expressing tumors may be equal or better targets (i.e., astrocytomas and head and neck cancers).

The results described here, and those reported by other investigators using labeled EGF (17), Tyr-3-octreotide (32), or vasoactive intestinal peptide (33), indicate that growth factors and related small molecules may improve current strategies of tumor localization and therapy. Although in vivo growth stimulation by natural growth factors needs to be examined carefully, advances in molecular biology techniques, such as site-directed mutagenesis, should facilitate the isolation of high-affinity variants acting as growth factor antagonists. In vitro evaluation should facilitate their selection for preclinical and clinical studies.

REFERENCES


Radiolocalization of squamous lung carcinoma with 131I-labeled epidermal growth factor.

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