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RADIOIMMUNODETECTION OF HEAD AND NECK CANCER

A review

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Radiolabeled antibodies can add a dimension in the diagnostic imaging and staging of metastatic head and neck malignancies. In the oral cavity, oropharynx and larynx the vast majority of malignancies are squamous cell carcinomas. This common cellular origin makes it feasible to search these neoplasms for appropriate tumor-associated antigens which can be used for radioimmunoscintigraphy. The pretherapeutic staging of head and neck malignancies, including salivary gland tumors, is based on clinical findings and conventional radiology (computerized tomography, magnetic resonance imaging, ultrasonography). The routine use of monoclonal antibodies for imaging head and neck malignancies was made possible by the production of several monoclonal antibodies to tumor-associated membrane antigens. A review of the clinical trials reported in the literature, and our own results with ^{111}In-labeled anti-carcinoembryonic antigen (CEA) antibody in 42 patients are presented.

Despite the rapid development of various radiological methods, e.g. computerized tomography (CT), magnetic resonance imaging (MRI) and ultrasonography (US) (1–10), it is still difficult to draw conclusions concerning malignancy with these methods since biopsy can be obtained. The specific diagnosis is usually comparatively simple in the head and neck area in patients with oropharyngo-laryngeal tumors. Immunoscintigraphy based on tumor-associated antibodies has the potential of increasing the sensitivity and specifity of tumor staging in head and neck malignancies, especially in the parotid glands and in neck regions where biopsies are not suitable.

Many monoclonal antibodies (MoAbs) against tumor-associated antigens have been examined in vitro in studies of head and neck tumors. The antigens are mainly related to the epidermal growth factor receptor and to various oncofetal antigens. In the oral cavity, oropharynx and larynx and vast majority of malignancies are squamous cell carcinomas. Squamous cell carcinoma (SCC) cell lines present several antigens, which have been studied experimentally with MoAbs (UM-A9, E48, SQM1, K931, K984, anti EGF-R1 receptor) in vitro and in animal models (11–24). Monoclonal antibodies directed against SCC of the head and neck are predominantly used in immunohistological techniques to confirm the epithelial origin of the malignant cells (11).

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Review of the literature

Experimental studies

The MoAb A9 has been tested in nude mice bearing different SCC-cell line xenografts (12), where it has shown specific radioimmunolocalization. Another MoAb (E48) has demonstrated highly specific tumor localization versus control MoAbs of the same immunoglobulin isotype in nude mice bearing an SCC xenograft derived from a head and neck carcinoma cell line (13, 14).

The MoAb SQM1, which recognizes a membrane protein is SCC, thought to be related to squamous cell differentiation and intercellular adhesion (15, 16), has been

studied in cell cultures. This antigen may also be the target for radioimmunolocalization, due to its involvement in cell differentiation. The MoAb K931 was produced to an antigen expressed in head and neck SCC, but not in normal squamous epithelium and tissues from these organs (17). This antigen was further characterized to represent the immunogenic epithelial 17-1A antigen (18).

The MoAb UM-A9 identifies an antigen, A9, which is expressed in SCC. Serum levels of this antigen may be related to prognosis, and are indicative of disease-free survival (19, 20). Fantozzi (21) has produced five MoAbs which are a highly specific to head and neck squamous cell carcinomas compared to non-malignant oral mucosal tissue: reactivity of Mab1, Mab2, Mab3, Mab4, and Mab5 in 10 oral squamous cell carcinomas was as follows: Mab1 9/10, Mab2 10/10, Mab3 8/10, Mab4 9/10, and Mab5 4/10, whereas in 17 non-malignant oral mucosal samples stainability with these Mabs was 6/18, 4/16, 5/18, 6/19 and 2/19 respectively. The monoclonal antibody K948 has been shown to significantly inhibit growth in a dose-dependent manner when SCC cells are grown in vitro in the presence of antibody. This antibody was also able to visualize tumor deposits in xenografted nude mice (22). The antigens expressed in SCC cell lines and recognized by the MoAbs K984 and K928 are regarded as novel markers associated with cellular maturation of the squamous epithelia (23).

The presence of phase-specific 44- and 200-kDa oncofetal antigens (OFA) was detected in 13 out of 15 patients with SCC and in 3/6 SCC cell lines using the MoAb 115 (24). These results also have implications for radioimmunolocalization.

Some OFAs, such as carcinoembryonic antigen (CEA), are synthesized by many different malignant cell lines, including different adenocarcinomas and carcinomas of epithelial origin in the head and neck area (25). Neoplastic well-differentiated squamous carcinoma cells from human oral mucosa have been found to generate a carcinoma expressing CEA in athymic mice (26). Several SCCs and adenocarcinomas in the head and neck regions express CEA.

A stable glycoprotein CEA (molecular mass approx. 200 kDa) is normally found in the fetal liver, pancreas and intestines during the first six months. The biological function of CEA is unknown, although it has been considered a tumor-associated but not a tumor-specific antigen in adults.

Monoclonal antibodies potentially useful for radioimmunoscintigraphy are listed in Table 1.

Table 1

Tumor-associated markers, and monoclonal antibodies raised against these markers, in head and neck malignancies

Antigen	Monoclonal antibody	Ref. No.
17-1A, epithelial cell surface	K931	17, 18
Basal membrane structure	UM-A9	19, 20
22-kD surface antigen	E48 F(ab')2	13, 14, 29
Poorly differentiated basal cells (50–55 kDa)	K984	22, 23
Highly differentiated suprabasal cells	K928	23
A-431 tumor cell line	UCD/AB 6.01	52
Cell lines 183A, 1483	MoAb R1-EGFR	54
Nuclear protein	Ki-67	53
Transferrin receptor	RPN-511	53
Cytokeratin-associated	174H.64	30
Membrane surface (48 kDa)	SQM1	15, 16
OFA (phase-specific 44 and 200-kDa antigens)	MoAb 115	24
CEA	anti-CEA-MoAb (clone F023C5)	36, 37 48, 49
GCDFP-15 (apocrine epithelia)	MoAb D6	41
Salivary gland	anti-BrdU MoAb	42
Salivary gland (cytokeratin)	PKK1	43

CEA = carcinoembryonic antigen
OFA = oncofetal antigen
GCDFP = gross cystic disease fluid protein

Clinical studies

Recently new antibodies against human SCC from the head and neck area have been developed (12–23), but not yet widely tested in the clinic. Some trials with MoAbs in imaging head and neck malignancies have been reported; in one such trial, I-131-labeled polyclonal anti-CEA antibody was used in five patients (27). Soo et al. (28) used ^{111}In-labeled MoAbs against the epidermal growth factor receptor in 11 patients with SCC of the head and neck. Positive images in 8 out of 11 patients were reported with no false-positives. Ten patients were studied by van Dongen et al. (29) with the ^{99m}Tc-labeled MoAb E 48 F(ab')$_2$, which reacts to squamous cell carcinoma. They reported sensitivity of 93% (38 of 41 tumor sites imaged) and two false-positive observations. Adams et al. (30) used ^{99m}Tc-labeled MoAbs 174H.64 against a cytokeratin antigen as an imaging agent in 55 patients.

There are several reports on the imaging of various malignant tumors with radiolabeled MoAbs raised against CEA (31, 32). The major application of anti-CEA antibodies has been in immunoscintigraphy of colorectal cancers (33, 34). This method has also been of importance for the imaging of advanced breast cancer and non-microcellular pulmonary cancer (35). Monoclonal ^{111}In-labeled anti-CEA antibodies have been used in 13 patients with oropharyngo-laryngeal epidermal carcinomas (36) and in 29 patients with parotid gland tumors (37). Timon et al. (38) used single-photon emission computerized tomography

Table 2

Pat. No./ age (y)/ sex	Diagnosis (Histology/site)	Immunohisto-chemistry /Imaging (ROI)	Tumor size (cm)
1 /71/M	SCC, Larynx R Rec (Tr)	Pos/1.3	7 × 7
2 /51/M	SCC, Larynx R	Pos/1.4	1 × 1
3 /63/M	SCC, Larynx R	Pos/1.7	1 × 2
4 /59/M	SCC, Larynx Neck mets R,L Rec (local)	Pos/1.6	2 × 2
5 /68/F	SCC, Epiglottis	Neg/2.1	2 × 2
6 /59/M	SCC, Piriform fossa Neck mets R	Pos/1.4	3 × $2\frac{1}{2}$
7 /67/M	SCC, Piriform fossa neck mets R	Pos/2.0	1 × 2
8 /60/M	SCC, Mesopharynx R Neck mets R	Pos/1.9	4 × 6
9 /69/M	SCC, Neck L Primary or metastatic?	Pos/1.6	7 × 8
10/63/F	SCC, baseos oris L	Pos/2.0	3 × 4
11/69/M	SCC, Tongue L Neck mets L	Pos/1.4	$\frac{1}{2}$ × $2\frac{1}{2}$
12/58/M	SCC, Tongue base R Neck mets R	Pos/1.3	1 × $1\frac{1}{2}$
13/69/F	Ca aden, Supraglottis R	Pos/1.2	$\frac{1}{2}$ × $\frac{1}{2}$
14/27/M	Hemangiopericytoma	Neg/2.2	5 × 4
15/66/M	Paraganglioma	Neg/1.6	$3\frac{1}{2}$ × $3\frac{1}{2}$
16/50/F	Acinic cell ca, Par	Pos/1.2	$3\frac{1}{2}$ × 3
17/37/M	Acinic cell ca, Par	Pos/1.3	1 × 1
18/56/F	Adenoid cystic ca, Par	Pos/1.2	2 × 2
19/67/M	Mets of adenoca, Par	Pos /1.2	2 × 2

ROI = region of interest
SCC = squamous cell carcinoma
mets = metastases
Rec = recurrence
TR = Tracheostoma
Par = parotid gland
R = right, L = left

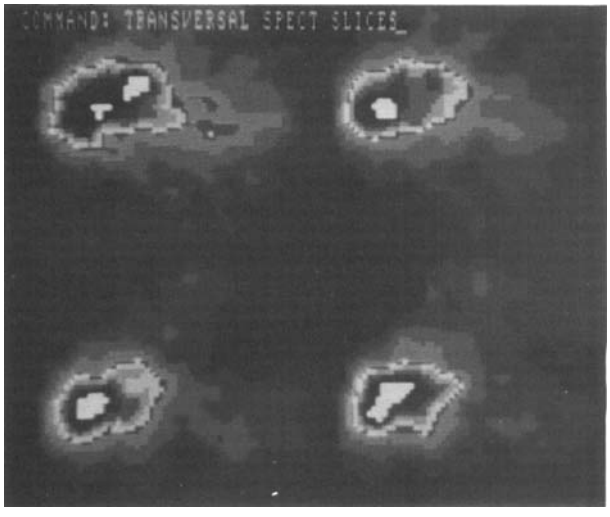

Fig. 1. SPECT study (four slices) showing intensive uptake in parapharyngeal soft tissue sarcoma (CEA negative immunohistochemically) using ^{111}In-labeled anti-CEA antibody 72 h after injection (tumor-to-background ratio 32 : 1)

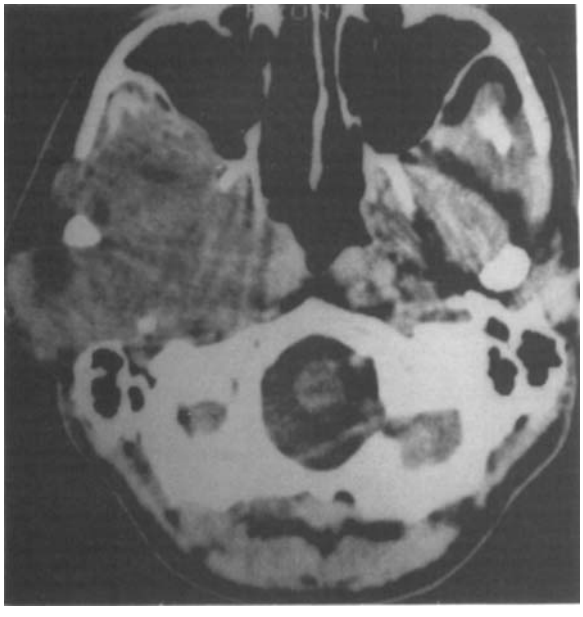

Fig. 2. CT-scan showing the same neoplasm as in Fig. 1.

(SPECT) with good results to study 7 patients with head and neck cancer. Imaging was done on the third day after the injection of ^{111}In-labeled anti-CEA antibodies.

The parotid gland

Radionuclide scanning with pertechnetate has been used in a limited number of patients to evaluate parenchymal function of the parotid gland (39). Warthin's tumors and the rare oncocytomas are radiopositive. Scanning with ^{99m}Tc cannot distinguish between benign and malignant salivary tumors, and ^{67}Ga localizes in normal salivary tissue (40).

Salivary gland tumors present diverse histopathological features and develop differently. Gross cystic disease fluid protein-15 is expressed in normal apocrine epithelia and is also present in tumors of the salivary glands. Swanson et al. (41) stained 133 sections of parotid gland tumors with MoAbs D6 against this protein, and found that benign tumors were more often stained (76% reactive) than malignant lesions (24% reactive). Anti-BrDu MoAbs have been used to observe the biological characteristics of salivary gland tumor tissues (42). Gustafsson et al. (43) used the monoclonal anti-cytokeratin antibody (PKK1) in salivary gland sections and suggested that cells in tumors should be characterized on the basis of their immunohistochemical staining properties, i.e., state of differentiation rather than their presumed histogenesis.

Theoretical evaluations based on the basis of affinity constants of the Ag-MoAb systems used, have shown

that it is possible to reach high tumor/background (T/B) ratios of up to 1 000 (44). The values obtained in patients are much lower, ranging from 2 to 5 (45). Under favorable conditions it is possible to detect a lesion when the T/B ratio reaches values of 1.4–1.9, but for a suitable image of a tumor, values higher than 2 are required (46).

Own investigation

Our research was designed 1) to evaluate on immunoscintigraphy method using an anti-CEA MoAb to detect primary tumors and their metastases in the head and neck area, and 2) to compare the results from immunoscintigraphy with surgical, conventional radiology and immunohistochemistry findings. Our study consisted of two groups of patients: Thirteen patients with oro/hypopharyngeal or laryngeal adeno/epidermoidal carcinomas (Group 1) (36), and 29 unselected consecutive patients with palpable unilateral tumor in the parotid gland region (Group 2) (37).

Radioantibody. The $F(ab')_2$ fragment of the anti-CEA antibody (clone F023C5) (Indomab-K-2, Sorin Biomedica, Saluggia, Italy) was labeled with ^{111}In ($InCl_3$ from Amersham International Ltd., U.K.). The dose of anti-CEA antibody fragment was 0.3 mg. The injected volume in physiological saline was approximately 3–5 ml. The activity injected varied from 52–100 MBq. The average specific activity was 260 MBq.

We observed no adverse reactions to the radioantibody. CEA in serum was measured in 40 patients, and only one presented elevated levels (>4 ng/ml). Elevated levels of the IgG and IgM subclasses of HAMA were observed in 5 and 27 out of 33 patients respectively.

Immunoscintigraphy. In Group 1 a total of 20 lesions were identified in the immunoscintigrams in 13 patients with oro-pharyngo-larynegeal carcinomas. The sensitivity detection rate (17/19) was 89% compared to surgical findings; correct configuration (primary tumor visualized separately with metastases) was obtained in 15 out of 19 known lesions. In Group 2 ten of the 58 parotid gland regions imaged were positive. Six of these positive findings were related to malignant tumors: two acinocellular carcinomas, one adenoid cystic carcinoma, one metastasis of adenocarcinoma of unknown origin, one soft tissue sarcoma and one paraganglioma. There were four positive non-malignant tumors. No negative scintigrams were associated with malignancy. Thus the specificity (17/21) and detection rate (6/6) as compared with the histological findings (to detect parotid malignancy) were 81% and 100% respectively.

Immunohistochemistry. In Group 1 11 out of the 12 SCCs, and the only adenocarcinoma, expressed positive immunohistological against CEA. All these tumors gave positive findings in immunoscintigraphic examinations. In Group 2 all the scintigraphically positive tumors (10/27) were immunohistologically stained for CEA. The positive tumors were acinic cell carcinomas, a metastasis of an adenocarcinoma (possibly of renal origin), and an adenoid cystic carcinoma. Paraganglioma and hemangiopericytoma were negative.

Tumor-to-background ratios T/B. In Group 1 all the tumors imaged presented positive radionuclide uptake. T/B ratios varied from 1.3 to 2.4. In one patient with a high hypopharyngeal uptake (T/B 2.1) in immunoscintigraphy the tumor was indentified histologically as an epidermoid carcinoma. Although it did not express CEA in histological staining. The patient had a recurrence after radiotherapy for supraglottical epidermoid carcinoma. One adenocarcinoma had low uptake (T/B 1.2) in immunoscintigraphy, and expressed CEA in histological staining. In Group 2 the T/B were low (1.2–1.3) in malignant tumors, except in patients with paragangliomas and hemangiopericytomas which showed strong tumor uptake in radioimmunoscintigraphy (T/B 1.6 and 2.2), but neither of these two expressed CEA in immunohistochemical studies.

Discussion

Most studies (12–23, 28–30) show that antibodies against epidermal growth factor receptor and SCC cell surface proteins may be useful in clinical radioimmunodetection. We have demonstrated a positive correlation between anti-CEA immunoscintigraphic and surgical findings for squamous cell and adenocarcinomas in the head and neck area. Tumor size could not be determined accurately from the radionuclide images, but the tumor site was generally in good agreement with radiological and surgical findings. Our results suggest that knowledge of the histological characteristics of the tumor before immunoscintigraphy facilitates the detection of possible metastases, if these express CEA. The antibodies to CEA may be of value especially in situations in which the primary tumor site is unknown, or when the patient is suspected of having a recurrence soon after operation, when previous surgery and possible postoperative radiation therapy may confuse the clinical picture and make subsequent examinations difficult. The value of using CEA for screening in immunoscintigraphy is limited although it is possible to detect malignant parotid tumors with anti-CEA immuno-scintigraphy.

In the parotid tumor group the route of antibody uptake was not apparent because there was no obvious relation between immunohistochemical and immunoscintigraphic findings. Serum CEA concentration did not correlate with our immunoscintigraphic findings. Radioantibodies absorbed in the reticuloendothelial system (RES) and retained in the blood pool interfered with the interpretation of the gamma images. The nasopharyngeal uptakes considered normal probably represent lymphatic tissues (RES) in these areas.

Immunoscintigraphy with ^{111}In-labeled anti-CEA antibody is a promising new tool that complements to MRI, CT, US and endoscopic methods in the staging of head and neck malignancies. Larger studies utilizing SPECT are needed for complete evaluation of the method (38). The possibility of detecting metastatic lesions at an early stage is still questionable, and should be studied further with longer follow-up periods.

The possible mechanisms of antibody uptake in tumors in vivo are not clear. A specific tissue CEA and the anti-CEA-antibody reaction seem not to be the only route of uptake, because large uptakes of radioantibody in tumors which did not express CEA in tissue specimens were observed. The non-specific uptake of immunoglobulins is probably due to the presence of the IgG-receptor in some tumors, causing non-specific uptake of radiolabeled antibodies without the expression of target antigens (47). In paraganglioma and parapharyngeal hemangiopericytoma we have demonstrated highly specific radioimmunolocalization (48, 49) without immunohistological evidence of antigen expression. However, we did not have the opportunity to use antibodies against anti-CEA antibody to immunohistologically localize the radioantibody in tumor specimens. The possibility that in vivo circulating antibody blocked all tumor-expressed CEA targets seems unlikely, although tumors with no CEA expression in immunohistochemical studies showed extraordinarily strong uptakes in immunoscintigraphic examination.

The anti-CEA MoAb we used seems to be associated with malignant tumors, but is apparently not specific for tumors expressing CEA. There are several possible paths of antibody uptake, and it remains for future investigations to study the non-specific processes involved in tumor localization with the anti-CEA or other tumor related MoAbs (50).

Monoclonal antibodies offer a potential for SCC imaging but many theoretical and practical problems are associated with their use (40). Potential radioimmunolocalization of cancer deposits by MoAb is valuable in the detection of lymph node metastases and recurrent tumors in the neck, and more specific biological tumor staging may also allow quantification of tumor load for therapeutic purposes. The possibility of selecting proper antibodies for the prompt determination of the viability of the tumor tissue, and for additional monitoring, may affect treatment modalities.

More effective loco-regional treatment, made possible with different routes of administration such as, e.g. immunolymphoscintigraphy (51) contributes to the increasing interest in the early diagnosis of distant metastases. At present the major problems seem to be the lack of specifity and the non-homogeneous uptake of the antibody by the tumor.

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