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REVIEW AND UPDATING

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Monoclonal antibodies for diagnosis and therapy of squamous cell carcimona of the head and neck

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INTRODUCTION

Squamous cell carcinoma represent the vast majority of all malignant tumours of the head and neck (80). They account for approximately 5% of all neoplasms in North-West Europe and the United States of America (5). A marked higher incidence can be found in Mediterranean and South American countries (60). In Brazil, 10.000 (7) and in the United States 41.200 new cases are diagnosed annually (62). SCC also represents the major histological type of neoplasms arising from lung, cervix and skin. Among lung tumours, 25-30% comprises of SCC and 50,000 new cases can be expected in 1992 in the U.S.A.. SCC of the head and neck (HNSCC) grow locally invasive and have a proclivity to metastasize to the regional lymph nodes rather than to spread hematogeneously to distant sites. Patients with cancer of the head and neck are classified according the TNM classification of the Union Internacional Contre le Cancer (UICC) or The American Joint Committee on Cancer (1, 28). After assessment of T, N, and M categories these may be grouped into stages. Small tumours (T1, T2) without lymph node involvement (NO) and distant metastases (MO) are classified as stage I and II, and the advanced cases as stage III or IV. Staging is important for treatment planning (3). Survival rates are directly linked to the tumour stage. Patients with a stage I or II have a relatively good prognosis, while patients with stage III or IV are much more difficult to treat curatively.

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The predictive value of neck node involvement on recurrence and survival in HNSCC is well known. It has been shown that the incidence in both neck recurrence and distant metastases is related to the number of tumour positive nodes and the extranodal spread (37, 65). A tumour that metastasizes to the regional lymph nodes may be a biologically more aggressive tumour than one that does not spread beyond its anatomic limits, and due to this biological characteristics may have an increased propensity to recur after treatment (25).

The improvements in surgical techniques and of radiotherapy have resulted in greater local and regional control in head and neck cancer patients in the last twenty years. For instance, the advent of modern reconstruction techniques has made wider excisions and thus more effective surgery possible. Nowadays, stage I and II head and neck disease is usually treated with surgery or radiation therapy alone, while patients with stage III and IV disease usually undergo combined surgery and radiation therapy. With these modalities loco-regional control can be achieved in the majority of patients (67). Unfortunately, as fewer patients die from uncontrolled disease above the clavicles, more patients are exposed to the risk of developing distant metastases and "second primary" tumours. Consequently, the overall cure rate for patients with head and neck cancer has remained stationary.

The overall clinical incidence of distant metastases in squamous cell carcinoma of the head and neck varies from 4.3% to 26% in different studies (25, 39, 43). Autopsy studies report on a much higher incidence of 40% to 57% (17-19). The lungs are the most frequent site of metastases, followed by the skeletal system (66).

This has caused a great interest in the development of adjuvant therapeutic modalities after surgery and radiotherapy.

However, the high expectations as to chemotherapy on these patients have not become true, and its application is limited to palliation of recurrent and metastatic disease (67, 69, 61). Development of more suitable diagnostic and therapeutic modalities for detection and treatment of metastic HNSCC is a major challenge in head and neck oncology. Monoclonal antibodies (MAb's) directed to tumour associated cell surface antigens are potentially powerful tools for diagnosis and therapy of HNSCC (11). Among the potential applications of such tumour-preferential MAb's is their use as targeting agents for the selective delivery of radionuclides to primary tumours and particularly to lymph node and distant metastases (18, 26). At present there is only a small number of monoclonal antibodies available which have been produced after immunization with head and neck cancer material. Recently we described the production of a panel of MAb's with a high affinity for membrane antigens expressed at the outer cell surface of SCC cells (50, 53). In this paper perspectives of MAb's for diagnosis and therapy of metastatic HNSCC are discussed.

Metastases of HNSCC

The understanding of the pathogenesis of metastases has increased considerably in the last two decades, but in head and neck cancer patients distant metastasis still remains a problem. The major obstacle to the eradication of metastases is that the cancer cells are biologically heterogeneous (21). The heterogeneity is manifested in a wide range of cell properties, such as cell surface receptors, karyotypes, morphology, growth properties and the ability to invade and produce metastases (15, 30). Although many neoplasms have an unicellular origin by the time of diagnosis, the lesions present an almost endless spectrum of heterogeneous properties. The process of cancer metastases consists of a serie of sequential, interlinked steps. Metastases begins with the invasion of tumour cells into host stroma surrounding the primary neoplasm. Tumor cell invasion into blood vessels and lymphatics is facilitated by production of enzymes such as cathepsin B and plasminogen activator (64), that can lyse basement membranes and host connective tissue. During local invasion and subsequent to arrest and attachment of metastatic cells in distant capillary beds, the tumour cells must penetrate blood vessels that surround blood vessels. During invasion, tumour cells can easily penetrate into small lymphatic vessels and be passively transported in the lymph to lymph nodes, where numerous lymphatic venous communications are found. Hence, tumour cells have the capacity of reaching the general circulation, as well as regional areas near their site of origin.

Clinical observations give the impression that carcinomas spread by the lymphatic route and mesenchymal tumours spread by the blood stream. This impression is erroneous, lymphatic and vascular systems have numerous connections (13). Experimentally, it has been shown that disseminating tumour cells may pass from one system to another (22, 82). During invasion by tumour cells the process of infiltration and expansion into host tissues results in the penetration of small lymphatic vessels. The release of tumour cell emboli into these vessels is responsible for lymphatic metastases. The regional lymph nodes (RLN's) can serve as effective, though temporary, barriers to tumour spread. Several mechanisms can alter the filtration capacity of lymph nodes. Tumour growth, acute or chronic inflammatory reactions or even local irradiation can reduce the efficacy of filtration. The RLNs may be involved immunologically in the host response to neoplasms. Experimental studies with radiolabeled tumour cells in rats have shown that most cells that reached the lymph nodes rapidly entered the efferent lymphatics and then the blood stream (70). The mere presence of tumour cells in the circulation does not constitute itself metastases, since most cells released into the blood stream are rapidly eliminated (58). Although most tumour cells are destroyed within the bloodstream, it appears that the greater the number of cells released by the primary tumour, the greater the probability that some cells will survive to grow out to metastasis (19). The number of tumour emboli in the circulation appears to correlate well with the size and clinical duration of the primary tumour. The development of necrotic and haemorrhagic areas within large tumours facilitates this process by providing tumour cells easy access to the circulation (20).

How exactly some tumour cells can survive in the blood stream is unknown, but some tumour cells can aggregate with each other (homotypic aggregation) or with host cells (heterotypic aggregation) such as monocytes, lymphocytes and natural killer cells (NK cells). Formation of such multicellular emboli assists the survival of tumour cells in the circulation. The most formidable obstacle to the treatment of single disseminated cells or cell clusters as well as established metastases may well be the heterogeneity of cells. The biological diversity of neoplasms implies that a successful treatment of the disease will require the total destruction of all tumour cells.

Selection of monoclonal antibodies for targeting HNSCC

Our attention focuses on the exploration of monoclonal antibodies for diagnosis and therapy of metastatic HNSCC.

Radioimmunuconjugates may be beneficial in the management of head and neck cancer patients in two ways: the assessment of the status of the lymph nodes in the neck and the detection and treatment of distant metastases. The relative superficial localization of the lymph nodes in the neck allows accurate radioimmunodetection in this area with a gamma camera. Since HNSCC have an intrinsic sensitivity for radiation, we give priority to the use of MAbs labelled with radioisotopes in radioimmunotherapy (RIT). However, this does not exclude the use of these MAbs as carriers for cytotoxic molecules like toxins and drugs at a later stage.

Recently, a panel of MAbs has been developed at our department selectively reactive with surface antigens present on HNSCC (50, 53). None of these MAbs are truly HNSCC specific, all show some reactivity with normal tissues. According to their reactivity on normal stratified squamous epithelia, they can be divided in four different groups. Characteristics of five representative antibodies and the antigens recognized by these antigens are summarized in Table I, and have been described extensively in literature. For selection of these antibodies we defined some selection criteria. A suitable antibody for tumour targeting is one which preferentially accumulates in the tumour after administration to the patient. Selectivity of antibody accumulation depends on antigen distribution and antigen accessibility. Ideally, antibodies should recognize antigens exclusively expressed in tumour tissue, but not in any normal tissue. In the selection of the MAb's mentioned above we envisioned that accessibility of antigen can make a MAb "operationally" selective for HNSCC targeting. In general the endothelium in normal squamous epithelium is particularly poorly permeable to macromolecules, while also the basement membrane on which the epithelial cells rest, as well as desmosomal junctions between the epithelial cells, form a serious barrier for antibody penetration. In contrast to normal squamous epithelium, HNSCC's can be characterized by the presence of fenestrated endothelium and defective basement membranes while the number of desmosomes may be decreased, especially in poorly differentiated tumours (10). These histological features are likely to make the access of antibody to HNSCC tumour cells more easy than to their normal counterparts.

Other selection criteria: the antigen should be located at the outer cell surface while its expression should be high in all HNSCC tumours, the antibody should be preferentially of the IgG class rather than of the IgM class, and it should not be reactive with blood cells, blood vessels or organs with expected high accessibility such as liver, spleen, and bone marrow.

For selection of just those MAb's directed to weakly immunogenic tumour associated antigens, a quick and reliable screening procedure was used (58). A primary screening was performed with cell ELISA's (48). MAbs were selected which bound to viable HNSCC, but not with ABO-erythrocytes.

Based on immunohistochemical data, MAb's E48, U36, K984, K928 are antibodies of choice for targeting to HNSCC, while K984, K928 and K931 provide favourable staining patterns for targeting to SCC of lung (60 a 74).

Table I.

Characteristics of monoclonal antibodies for targeting HNSCC

	E48	U36	K928	K984	K931
reactivity with normal squamous tissue	**basal and suprabasal**	**basal and suprabasal**	**suprabasal**	**basal**	**none**
HNSCC (0% pos.)	3/58 (5%)	0/60 (0%)	1/60 (2%)	2/59 (3%)	7/55 (13%)
HNSCC (<10% pos.)	5/58 (9%)	1/60 (2%)	3/60 (5%)	3/59 (5%)	12/55 (22%)
HNSCC (10-50% pos.)	12/58 (21%)	4/60 (6%)	8/60 (13%)	10/59 (17%)	15/55 (27%)
HNSCC (51-95% pos.)	25/58 (43%)	43/60 (72%)	42/60 (70%)	41/59 (70%)	19/55 (34%)
HNSCC (>95% pos.)	13/58 (22%)	12/60 (20%)	660% (10%)	3/59 (5%)	2/55 (4%)
Mol. weight antigen	22 kD	200 kD	50kD	90 kD	37 kD
Affinity constant (M^{-1})	3×10^{10}	7×10^{10}	7×10^{9}	1×10^{10}	3×10^{1}

At this institute, MAb E48 has obtained priority for further development to clinical application in HNSCC diagnosis. MAb E48 recognizes a 20-22 kD antigen which is involved in the structural organization of squamous epithelia, possibly at the level of cell-cell adhesion (59).

Perspectives of monoclonal antibodies for diagnosis of HNSCC

In head and neck cancer patients, the status of the cervical lymph nodes has been recognized as the most important prognostic factor (65). Clinical assessment of the status of the neck lymph nodes is still a problem. It is mainly based on palpation, and the overall error in assessing the presence or absence of neck node metastases from palpation alone is reported to be in the range of 20-30%(2, 57). Modern imaging techniques like magnetic resonance (MRI), computer tomography (CT), and ultrasonography (US) are more objective but have limitations for detection of small lymph nodes, whereas often these techniques can not discriminate between normal nodes, reactively enlarged nodes and tumour infiltrated nodes. Recently, a comparative study between the modalities mentioned above, showed that the US-guided fine needle aspiration cytology (FNAC) is the most accurate method for diagnosis of lymph node metastases, with an accuracy of 92% (75). However, this latter technique strongly depends on the skill of the operator, while it has no value in diagnosis of distant metastases.

Difficulties for accurate assessment of the status of the neck nodes leads to both over- and undertreatment of the neck. Therefore, more suitable modalities for detection of metastases are needed. Recently, the capacity of ^{131}I-labelled MAb E48 for radioimmunolocalization of HNSCC xenografts grown in nude mice was demonstrated, warranting clinical evaluation of MAb E48 for tumour detection in HNSCC patients (49).

Of major concern when designing a first clinical protocol for the evaluation of the diagnostic accuracy of an antibody, is the choice of the radioimmunoconjugate to be used. Conjugates of smaller fragments like $F(ab')_2$, Fab, Fv, or FH produced by enzymatic digestion or genetic engineering (55) seem to be more attractive for tumour diagnosis than whole IgG because; (a) fragments are cleared more rapidly froom blood than whole IgG resulting in lower background activity and reducing the radiation dose to normal tissue, (b) the smaller size of fragments should allow better tumour penetration than whole IgG, and (c) fragments lack the Fc region responsible for non-specific tissue uptake by Fc receptor binding cells and may be less immunogenic in humans. Nevertheless, the absolute uptake of fragments is lower for fragments than for the whole IgG molecule. Comparative studies on MAb E48 IgG and $F(ab')_2$ in HNSCC bearing nude mice revealed superior localisation and imaging with MAb E48 $F(ab')_2$ fragments (23). Some radionuclides under present investigation in clinical radioimmunoscintigraphy (RIS) are summarized in Table II.

Tabela II.

Radionuclides used for tumour-targeting:¥-emitters for radioimmunoscintigraphy and ß-emitters for radioimmunotherapy

Isotope	Half-life time	Clinical use
Gamma-emitters		
Iodine-131	8 days	imaging
Iodine-123	13 hours	imaging
Indium-111	68 hours	imaging
Technetium-99m	6 hours	imaging
Beta-emitters		
Iodine-131	8 days	therapy
Yttrium-90	64 hours	therapy
Rhenium-186	91 hours	therapy
Copper-67	62 hours	therapy

Several comments can be made on applicability of these nuclides in radioimmunodetection of HNSCC. 131-Iodine and 123-Iodine labels are not favourable because dehalogenation of antibodies will result in isotope uptake in the thyroid which may disturb tumour imaging. Similar considerations can be made for detached 111-Indium which may accumulate in lymphocytes present in the lymph nodes.

It can not be expected that improvements of labelling methods will resolve these problems shortly. High costs (111-In, 123-I), extensive radiation exposure to the patient (111-In), limited availability (123-I), long half life time (131-I), and poor imaging qualities (131-I) can be other draw-backs. 99m-Technetium has many advantages over the previously mentioned isotopes because the minimal radiation delivery to the patient (short half-life time and low gamma energy), its ideal properties for gamma cameras (high photon abundance), low costs and good availability. Better and more simple labelling methods for 99m-Technetium have recently become available (42).

Recently the diagnostic value of i.v. administered ^{99m}Tclabelled murine E48 F(ab')$_2$ was evaluated in 10 patients with a histologically proven squamous cell carcinoma of the head and neck and with clinical evidence of cervical lymph node involvement (73). Preoperative findings on lymph node status obtained by RIS, CT, MRI and palpation were defined per side (left and/or right side of the neck) as well as per lymph node level (I through V) and compared with the histopathological outcome of the neck dissection specimen.

In 10 patients, all 8 known tumours at the primary site were detected by RIS.Furthermore, RIS was correct in 13 of 13 tumour involved neck sides in 17 of 20 tumour involved lymph node levels. False negative observations comprised 3 levels containing tumour deposits smaller than 1 cm in diameter, 2 of which were not detected by any other diagnostic modality. Palpation, CT, and MRI were correct in, respectively, 13, 15, and 15 of the 20 tumour involved levels. In two patients RIS provided clinically important information which was not provided by any other diagnostic method. In one patient, recurrence was established of laryngeal carcinoma at the primary site after previous radiotherapy. In another patient, bilateral instead of unilateral lymph node involvement became apparent. These data indicate that RIS with MAb E48 may be helpful in the diagnosis of metastatic and recurrent head and neck cancer.

Perspectives of monoclonal antibodies for tumour therapy : general considerations

Presently, much interest is focused on the potential of MAbs in treatment of cancer. Research on the therapeutic utility of MAbs is characterized by its great diversity. In some approaches unconjugated antibodies are being used for elimination of tumour cells. The rationale for their use is that immunological effector mechanisms like antibody dependent cellular cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC) can serve as a cytotoxic modality, or that MAbs block tumour-associated processes like proliferation and metastases, by binding to cell-surface receptors directly involved in these processes. In other approaches, MAbs are used as targeting agents for selective delivery of chemotherapeutics, toxins, enzymes, or biological modifiers. A third line of research employs bispecific antibodies, which possess two different antingen-binding specificities, one directed against the tumour cell, the other directed against a radioactive hapten, an enzyme, or a cell surface molecule on an effector cell, like cytotoxic T-cell or K/NK cell. Most clinical experience has been obtained in the usage of unconjugated and radiolabeled mouse MAbs.Unmodified antibodies have demonstrated efficacy in some cases (40). The best results, including complete remissions, have been observed in patients with haematological malignancies (31). Tumours in lymph nodes and solid tumours were generally found refractory to treatment. However, in most of these trials, the patients were in advanced stages of disease and often immunodeficient. As animal studies have shown, therapy with unconjugated antibody may be considerably more effective in the case of minimal disease than in case of well established tumours or widely disseminated disease (44).

An argument to use radiolabeled MAbs is the heterogeneity in antigen expression and/or the heterogenous penetration of the antibody in solid tumours. It is unnecessary for radiolabeled MAbs to bind to each single tumour cell to achieve maximal therapeutic effects. This is especially true for ß-particle emitting radionuclides which are cytotoxic at a distance of several diameters. Up to this moment the ß-emitters 131-Iodine and 90-Yttrium are the most widely used isotopes in clinical RIT studies. Advantages and disadvantages of these isotopes have been clearly documented. ^{131}I is easy to label and has an appropriate physical half-life (8 days), particle energy (ß; E_{max}, 0.8 MeV) and path length (r_{90} = 0.83 mm in which r_{90} is the radius of a sphere in mm in which 90% of the energy of a point source is absorbed) (63). A problem with ^{131}I is the instability of the radioimmunoconjugate, both in serum and at the tumour site (4). Another problem is the ¥ -emission which represents 65% of the released energy and poses hazard to the patient and to medical personnel. ^{90}Y has the advantage of high particle energy (ß;E_{max}, 2.2 MeV), comparatively long path length (r_{90} = 5.34 mm), and an appropriate physical half-life (2.7 days). For binding ^{90}Y to an antibody, the chelate DTPA has been used most frequently.

The antibody-chelate conjugate appeared instable, resulting in sequestering of ^{90}Y in non-target organs like spleen, liver and especially bone marrow (76). Absence of imageable ¥ -emission, which is hepful for monitoring tumour targeting and dosimetry estimates is another disadvantage of ^{90}Y (61). Most recently, the conjugation of ß-emitters such as 67-Copper, 153-Semanium, and 186-Rhenium has become possible, opening avenues for effective RIT.

Our laboratory recently developed stable ^{186}Re-antibody conjugates which will be tested in RIT studies shortly. The half-life of ^{186}Re is 3.7 days. ^{186}Re has an ideal ¥-emission for imaging. The energy (ß;Emax, 1,07 MeV) and path length (r_{90} = 1.8 mm) make ^{186}Re an excellent candidate radionuclide for RIT in patients with minimal disease.

In clinical trials on the efficacy of RIT, complete and partial remissions were obtained in a proportion of patients with hepatoma using ^{131}I-labelled polyclonal antiferritin (46), Hodgkin's lymphoma using the same antiferritin antibody either ^{131}I- or ^{90}Y-labelled (38, 79), non-Hodgkin's lymphoma using ^{131}I-Lym-1 (12), cutaneous T cell lymphoma using ^{131}I-T101 (56), melanoma with ^{131}I-p97 F(ab')$_2$, (8), ovarian cancer with ^{90}Y-labelled MAbs (16, 68), leukaemia (47), and colorectal cancer (54).

A major obstacle in RIT is the low specific uptake in human solid tumours, which is typically 0.001% to 0.01% of the injected dose per gram (%ID/gr) of tissue (17, 27).

Such amounts are not sufficient to deliver enough radiation to the tumour. Uptake levels of 0.01% to 0.1%, as we find for MAb E48 in HNSCC patients are exceptions (35). The current status of RIT has been clearly formulated in a recent report of the European Association of Nuclear Medicine Task Group on the clinical utility of labelled antibodies: "The percentage of injected dose taken up is still an order of magnitude to low, and therapeutic ratios are still very low. At present the technique is most successful in microscopic disease" (6). This latter observation can be explained by biodistribution data as provided by Chatal et al. (9). They reported on the biodistribution of OC125 i.p. injected into patients with ovarian carcinoma, demonstrating low accumulation in large tumours (0.0014-0.0032%ID/gr), but significantly higher uptake in small nodules (0.13±0.08%ID/gr), and malignant cell clusters (median 0.33 with a maximum dose of 4.16%ID/gr). They explained the higher uptake by the better accessibility of antigen in small tumours than in large tumours. These data indicate that RIT with MAbs directed against HNSCC may be a feasible appraoch especially as adjuvant therapy.

Perspectives of monoclonal antibodies for tumour therapy of metastatic HNSCC

The group of HNSCC patients at high risk of developing distant metastases has been clearly defined at our institute. In order to identify risk factors predicting the development of distant metastases, Leemans et al. analyzed a group of 281 patients with HNSCC who did not develop recurrent disease above the clavicles (36). All patients were primarily operated and received postoperative radiotherapy when three or more tumour infiltrated neck lymph nodes were found upon pathological examination. The 5-years overall incidence of distant metastases in this group was 10.7%. The number of involved nodes appeared to be an important prognostic factor: when 3 or more nodes contained tumour, the change of developing distant metastases was found to be almost 50%. In addition, with the presence of extranodal spread, the change of developing distant metastases increased dramatically (3 times more metastases than in patients without extranodal spread). Even more unfavourable percentages are seen when patients are included who develop recurrent disease at the locoregional site: at least a doubling of the incidence of metastases is seen (34, 43). A realistic option to improve adjuvant therapy for this group of head and neck cancer patients a high risk of developing distant metastases is the use of radiolabeled monoclonal antibodies.

Recently, we reported on a first experimental study on RIT in HNSCC. ^{131}I-Labelled MAb E48 IgG was shown to be highly capable of eradicating human HNSCC xenografts in tumour bearing nude mice (24). A 4.1-fold increase in the median tumour volume doubling time and regression of 2 out of 10 tumours (20%) was observed in mice treated with 400 µCi ^{131}I-labelled MAb E48 IgG. In mice treated with 800 µCi, 2 out of 7 tumours (29%) showed complete remission without regrowth during follow-up (> 3 months). Median tumour volume doubling time in the remaining 5 tumours was increased 7.8-fold. In the same xenograft model, chemotherapy with doxorubicin, 5-fluorouracil, cisplatin, bleomycin, and methotrexate yielded a less profound anti-tumour effect. No cures were observed with any of the chemotherapeutic agents. This data suggest RIT with MAb E48 to be a potential therapeutic modality for the treatment of HNSCC. First clinical trials to test the therapeutic efficacy of RIT in HNSCC patients can be expected in the near future.

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RESUMO

O grupo de carcinomas espinocelulares da cabeça e pescoço em pacientes com alto risco de desenvolver metástases à distância, tem sido bem definidos do ponto de vista prognóstico em nossa instituição. Com intuito de selecionar fatores de risco preditivos no desenvolvimento de metástases à distância, Leemans e col analisaram um grupo de 281 pacientes com carcinoma epidermóide que não desenvolveram doença recorrente acima da clavícula (79). Todos os pacientes foram primariamente operados e submetidos à radioterapia complementar diante de 3 ou mais linfonodos histológicos metastáticos na avaliação da peça operatória, sendo que neste grupo, a incidência de metástases à distância a 5 anos foi de 10,7%. O número de metástases em linfonodos em nº de 3 ou mais, foi determinante do desenvolvimento de metástases à distância em 50% dos casos, fato este não detectado quando esta cifra estava abaixo de 3 linfonodopatias. Em contrapartida, a presença de ruptura extra-capsular foi um fator dramático de mudança de prognóstico no que diz respeito à presença de metástases à distância (3 vezes mais que nos casos onde a ruptura extra-capsular estava ausente). Outro aspecto que mereceu a atenção dos autores, foi aquele relacionado com os pacientes recidivados loco-regionalmente ocorrendo nestes pacientes duas vezes mais metástases sistêmicas (80,81). A opção proposta no sentido de introduzir uma terapia adjuvante para os pacientes com alto risco de desenvolver metástases à distância, é o emprego de anticorpos monoclonais marcados.

Recentemente, apresentamos um primeiro estudo experimental em carcinoma epidermóide da cabeça e pescoço tratados por radio-imunoterapia. Foi demonstrado que a IgG E48 de anticorpos monoclonais marcados com I^{131} foi capaz de eliminar implantes humanos de carcinoma escamocelular em tumores transplantados para ratos(82). Em 20% dos experimentos desenvolvidos (2 em 10 tumores), foi observada uma regressão em ratos tratados com 400μCi de IgG E48 de anticorpos monoclonais marcados com Iodo 131 tratados com 800 μCi, 2 em 7 tumores(29%) mostraram completa remissão sem recidiva durante o seguimento (> 3 meses). Nos mesmos casos, a utilização de quimioterapia com doxorubicina, 5 fluor-uracil, cisplatinum e methotrexate exibiram uma resposta menor, demonstrando um efeito antitumoral mais fugaz, não ocorrendo nenhuma cura com o emprego de antiblásticos. Este dados sugerem que o emprego da radio-imunoterapia no tratamento do câncer da cabeça e pescoço, pode se transformar numa nova alternativa no tratamento das lesões com altas capacidade de recidiva e disseminação.