Radioimmunoguided Surgery in the Treatment and Evaluation of Rectal Cancer Patients

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Several therapeutic options are available for the treatment of rectal cancer. To determine the most appropriate method of treatment, Radioimmunoguided Surgery (RIGS) can be used as an intraoperative diagnostic tool and as an adjuvant to traditional methods for more accurate staging. RIGS employs radiolabeled monoclonal antibodies directed against tumor-associated antigens and a gamma-detection probe to discriminate between normal and abnormal tissue. Most patients with primary or recurrent rectal cancer are considered good candidates for surgery using RIGS scanning. Use of the RIGS system may result in improved patient survival through accurate assessment of extent of disease and the selection of appropriate therapy. Prospective studies are necessary to define the optimal use of this approach as an experimental and clinical tool.

Introduction

Several therapeutic options for the treatment of rectal cancer - abdominal perineal resection vs low anterior resection, radical resection vs transanal resection, preoperative vs postoperative radiation, chemotherapy vs radiation therapy - engage both the science and the art of surgery. While certain criteria point to the use of one surgical option or another, a treatment plan often is selected without establishing the true extent of disease. In rectal cancer more so than in colon cancer, choosing the correct option for an individual patient is important since the issue of permanent colostomy has to be addressed.

Radioimmunoguided Surgery

Radioimmunoguided Surgery (RIGS) is an investigational technique that can be used to more accurately define the extent of disease and to select the most appropriate therapeutic option. RIGS technology consists of a murine monoclonal antibody (MAb), CC49, radiolaabeled with a low-energy, gamma-emitting isotope, iodine 125 (I-125), and a hand-held, gamma-detecting probe (the Neoprobe 1000 instrument). Additional information on the engineering and physics of the system has been described in greater detail elsewhere.[1]

For the past decade, we have been using RIGS technology as an investigational technique at our institution. Most patients with primary or recurrent rectal cancer are good candidates for surgery using RIGS scanning. Approximately three weeks prior to surgery, the CC49/I-125 complex was injected into patients. For the purposes of the phase I, II, and III studies, a traditional surgical exploration was performed using inspection and palpation, which was followed by a RIGS examination by scanning for any “hot” areas. All RIGS-positive areas were removed if possible. After surgical extirpation, the probe was used to check the bed of resection and the margins to determine RIGS status. In a small number of rectal cancer patients, we used transanal scanning preoperatively to select those patients who would benefit from a local resection.

CC49 MAb

CC49 is a second-generation, antitumor-associated glycoprotein (TAG-72) developed at the National Cancer Institute[2] for use with RIGS. The reactive antigen, TAG-72, has been purified and found to have a high affinity for sialomucin with a high molecular weight (Mr $\leq 10^6$). It is expressed on most human colon and rectal cancer lines with minimal cross reactivity to normal human adult tissues. Other anti-TAG antibodies used with RIGS have been the first-generation murine monoclonal, B72.3, and the second-generation murine monoclonal, CC83.[3] The greater affinity of CC49 for human colon and rectal cancer cells and the positive clinical results make this the antibody of choice. The dose of CC49 usually is 1 mg.

Iodine 125

Of the many radioisotopes available, the low-energy I-125 is the most useful. Its long half-life of 60.2 days (compared to other commonly used, medically useful radionuclides) is preferred for the labeling of CC49 MAb, which requires 14 to 21 days or more to reach optimal pharamacokinetics for tumor localization. The radiolabeling process is done by the lodo-Gen method. With its low gamma emission of 35keV, I-125 cannot be externally scanned for patient imaging, unlike I-131 or technetium. The current dose of I-125 is 2 mCi.

Hand-Hand Gamma-Detecting Probe

The hand-held gamma-detecting probe contains a cadmium telluride crystal optimized for detection of low-energy radioisotopes. Because there is no high-energy radiation, little scattering is produced and collimation is not needed, thereby permitting close discrimination between normal and abnormal tissues. The probe is internally designed to squelch at three standard deviations above the mean background. A preprogrammed five-second count is performed to set the squelch background level. For intraoperative scanning, two-second counts are obtained. Any count three sigma over background (positive for RIGS) results in a high-pitched sound, which prevents the false targeting of background tissues.

Surgical Technique

The use of RIGS scanning is contraindicated in patients with medical conditions that cannot permit a three-week wait from the time of injection to the time of surgery. Examples include patients with an impending bowel obstruction or significant blood loss. After the thyroid is blocked (THYROBLOCK), the radiolabeled MAb is injected. Two-second precounts are obtained with the probe to determine the radiolabeled antibody clearance. Generally, the initial counts are in the range of 2000 to 4000 counts per two seconds. Because the biologic half-life for CC49/I-125 is approximately three days, the surgery date is set approximately three weeks hence with the certainty that 95% of patients will have cleared by that time (Fig 1). Patients who wish to be operated on sooner should be checked at two weeks, as many will have cleared the radioactive antibody complex systemically by that time. Prior exposure to a murine MAb and the presence of human antimouse antibody may accelerate clearance and allow an earlier operation.

The typical RIGS surgical procedure begins as a traditional procedure with a midline incision. A traditional surgical exploration using inspection and palpation is performed.
The surgeon then commits to traditional intraoperative findings. For the purposes of the phase I, II, and III studies, the abdomen is divided into four zones: the liver; the abdomen above the pancreas except the liver; the mid-abdomen below the pancreas; and the pelvis.[4] The RIGS examination is then performed by carefully scanning all four zones. Any “hot” areas (ie, RIGS-positive tissue) are removed for biopsy, if possible, and the results are recorded. The surgery then proceeds either as planned or as reconsidered based on new RIGS-generated information. After surgical extirpation of tumor, the probe is used to check the bed of resection and the margins to determine the new RIGS status. Positive and negative findings are recorded.

This protocol was developed for the purposes of clinical studies. However, when the RIGS system becomes commercially available, we believe the probe will be used immediately in order to define the extent of disease and to augment the surgeon’s visual and tactile senses in an additional intraoperative information. While there is little difference between using RIGS in a patient with colon cancer or in a patient with rectal cancer, some technical aspects of rectal cancer cases warrant further explanation.

Preoperative Scanning

The use of rectal ultrasound for preoperative staging of rectal cancers is becoming more common in many centers. With good technique, the depth of invasion can be determined with reasonable accuracy and the presence or absence of potential metastatic lymph nodes can be visualized.[5] This information is often used to determine if preoperative radiation therapy should be added to the treatment plan. This experience led to our interest in using the probe for transanal examination prior to beginning the operative procedure.

The pelvis, shaped as a bowl with transrectal, transvaginal, and transsacral access, seemed ideal for RIGS scanning (Fig 2). Five patients with rectal cancer were considered for transanal excisions of small lesions (Table). They appeared to meet traditional criteria for transanal excision, ie, lesions were small (less than 3 cm) and exophytic, and all had been enrolled in a RIGS study. Each patient was examined transanally with rectal ultrasound and the gamma-detecting probe. The probe suggested pelvic metastatic disease in three of the five patients. These three underwent abdominal perineal resection of the rectum. Routine pathologic examination with hematoxylin and eosin confirmed the probe findings in two of these three patients. One patient with a 2-cm lesion had 18 of 18 positive nodes that were not visualized with computed tomography (CT) scan or rectal ultrasound. Another patient had metastatic disease to the iliac lymph nodes. The remaining two patients underwent transanal excision as planned and remain disease-

Rectal Cancer Detection

Future prospective studies and experience with the RIGS system may help to define the optimal use of the probe with rectal cancer. We believe that the behavior of the disease and the range of treatment options available make RIGS a valuable technique for directing patient management. Rectal cancer spreads through direct extension, lymphatic spread, hematologic spread, or peritoneal seeding. Current treatment is directed toward controlling these processes. The lateralization of tumor spread, either through direct extension or lymphatic flow, has convinced many surgeons to consider an extended mesorectal resection as part of a standard low anterior resection, and some evidence indicates that this is beneficial. However, this procedure is more extensive and is associated with additional complications. Also of interest is extended ileopelvic lymphadenectomy. Both of these approaches can be strengthened with proper patient selection, and RIGS may help in this area.

The operative procedure should be tailored to preoperative and intraoperative findings of all the diagnostic methods used rather than to a single standard approach. Diagnostic modalities include physical examination, rectal ultrasound, CT scan or magnetic resonance imaging, traditional intraoperative findings, and gamma-detecting probe findings. For example, if the tumor is small on physical examination, is limited on rectal ultrasound with no lymph nodes, shows no evidence of metastatic spread on CT scan, and shows no evidence of spread with RIGS, then a local resection is performed and the patient is closely followed. However, if the disease appears to be limited except for RIGS-positive activity in the pelvis, then a formal resection is performed with a lymph node dissection directed by the gamma-detecting probe. If RIGS activity is present along the iliac vessels, we include this area in the dissection; if no RIGS activity is found, it is left alone. We believe that the probe helps to direct the extent of the operative procedure. RIGS-positive activity in lymph nodes is a sound indication of the extent of tumor spread and that these abnormal nodes need to be removed completely if curative intent is desired.[4] If the RIGS activity is too extensive, then a limited resection is undertaken as a palliative procedure.

Conclusions

Our investigation supports the intraoperative use of RIGS as an additional technique to assess the extent of tumor spread and metastatic disease in patients with colon and rectal cancer. RIGS not only clarifies the choice of appropriate therapeutic interventions by providing immediate intraoperative data, but also presents a reliable preoperative staging technique that impacts on adjuvant therapy and, ultimately, on patient survival. Further study of RIGS is warranted to establish its limits and to explore its potential to enhance the surgical ablation of colon and rectal cancer.

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References
