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CT assessment of esophageal carcinoma response to neoadjuvant chemotherapy according to WHO and RECIST guidelines

The incidence of adenocarcinoma of the esophagus is rising faster than any other malignancy. The prognosis of esophageal carcinoma is poor (10,11,12).

The most common presenting symptoms of esophageal cancer are dysphagia and weight loss. Less common symptoms include odynophagia, cachexia, melena, retrosternal pain, and hoarseness. Cancers of the esophagus must involve at least 75% of the circumference before the sensation of food "sticking" or blockage is experienced. Because of that, about one-half of esophageal cancer patients present with locally advanced unresectable disease or distant metastasis (8).

Single-modality or multi-modality therapy may be applied in patients with esophageal carcinoma. Chemotherapy, radiotherapy and surgical resections may be used (3,15,16). Surgical esophagectomy remains the preferred treatment for clinically localized thoracic esophageal carcinoma (3,8,11). Both chemo- and radiotherapy may be used as pre- or post-operative treatment (4).

The evaluation of changes in neoplastic lesions in response to pharmacological treatment is an increasingly important task for radiologist (1). Nowadays therapy response may be assessed according to WHO and RECIST criteria.

The aim of the study was presenting the use of CT in evaluating esophageal carcinoma response to neoadjuvant chemotherapy according to WHO and RECIST criteria.

MATERIAL AND METHODS

The material comprises a group of 47 men (aged 35–72 years) and 5 women (aged 40–54 years) with diagnosed esophageal carcinoma. In all patients CT examination of the esophagus was performed, using CT scanner Somatom AR. T by Siemens, in 5 mm thick axial sections before and after administering contrast agent intravenously and orally. The control CT examination was performed in each patient after the proper course of neoadjuvant chemotherapy, using the same scanning protocol.

RESULTS

Adenocarcinoma was found in 16 patients and squamous cell carcinoma in 36. Twenty-five patients were in clinical stage IIA, 5 patients in stage IIB and 22 patients were in stage III. The narrowing of the esophageal lumen was found in 51 patients, with dilatation above the narrowing in 30 of them. The thickness of the esophageal wall was between 5–25 mm.

After chemotherapy the complete CT response was found in 6 patients (11.54%). The thickness of the esophageal walls were below 5 mm, (Fig. 1), and retention of contrast visible before chemotherapy was not seen (Fig. 2), and in 3 of them it was a complete histopathological response. In 15 patients (28.85%) the partial response was found (Fig. 3). In 21 patients there was no change

after chemotherapy, and in 10 the progression was found (Fig. 4). According to RECIST criteria the total response was found in 6 patients, partial response in 17, and stable disease in 24 and progression in 5 of them (Fig. 5). The assessment of the complete response was identical according to both WHO and RECIST guidelines (Fig. 6). Only in assessment of the progressive diseases (PD) the differences were statistically significant ($p<0.05$). Local lymph node enlargement was found in 23 patients. In 4 of them there was enlargement of multiple lymph nodes. After chemotherapy the enlarged local lymph node were found in 17 patients.

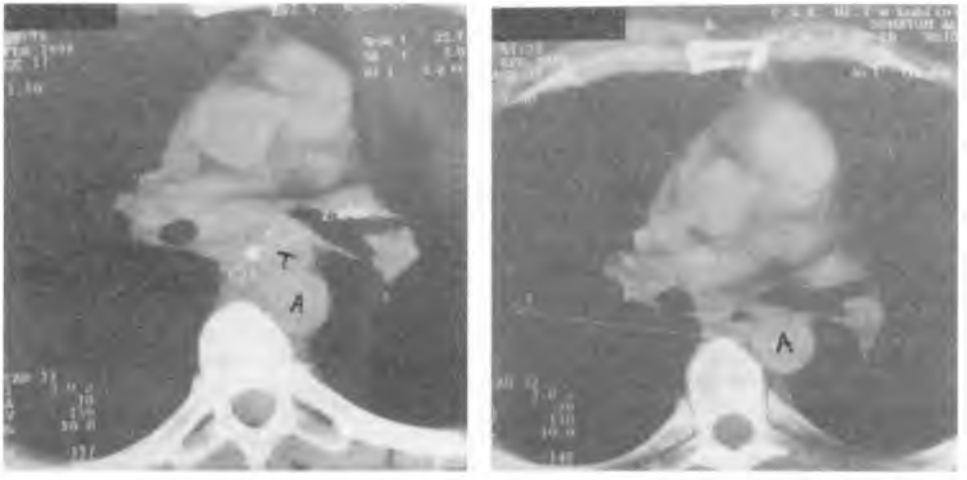

Fig. 1. Complete response to chemotherapy before – A, and after therapy – B; thickness of the esophagus after operation below 5 mm (T – tumor, A – aorta)

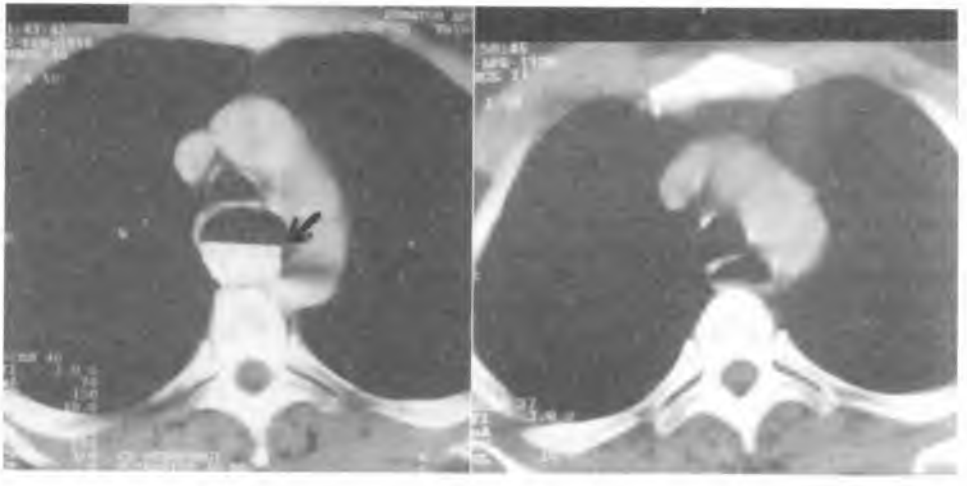

Fig. 2. Complete response to chemotherapy before – A, and after therapy – B, retention of contrast above the tumor visible only before therapy

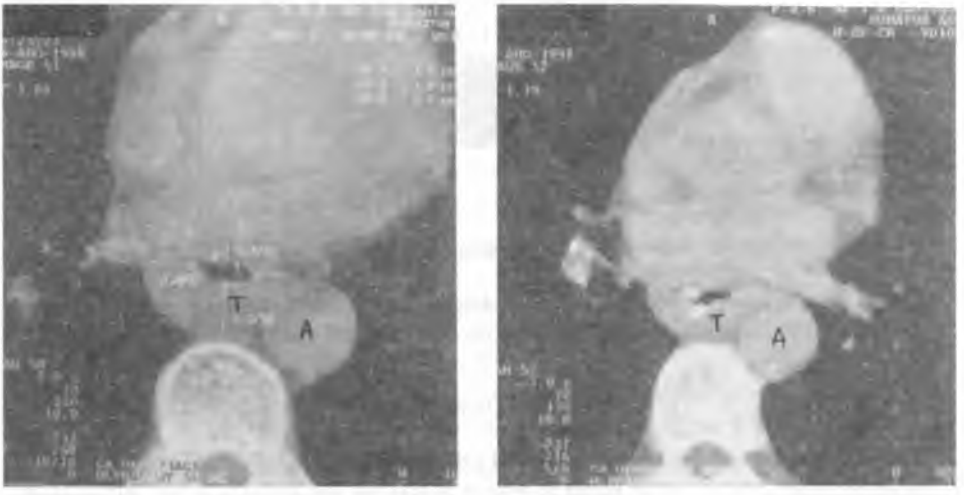

Fig. 3. Partial response to chemotherapy before – A, and after therapy – B, (T – tumor, A – aorta,)

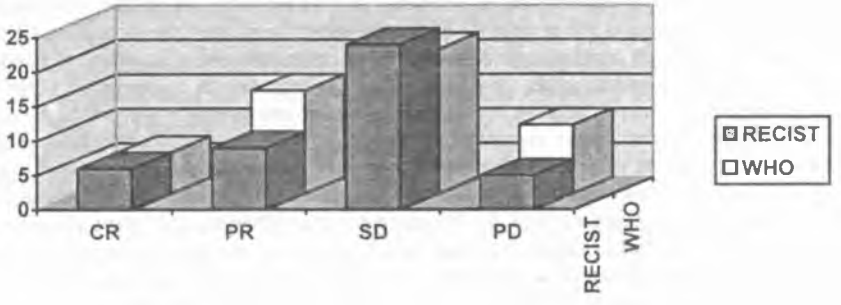

Fig. 4. Comparison of the therapy response assessed according to WHO and RECIST guidelines (CR– complete response, PR – partial response, SD– stable disease, PD – progressive disease)

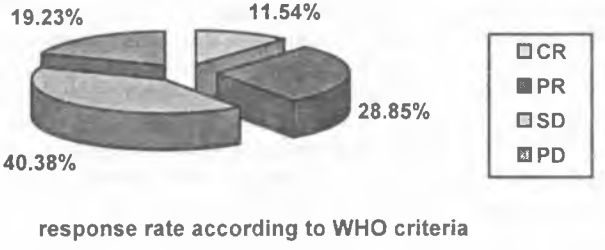

Fig. 5. Therapy response assessed according to WHO (CR – complete response, PR – partial response, SD– stable disease, PD – progressive disease)

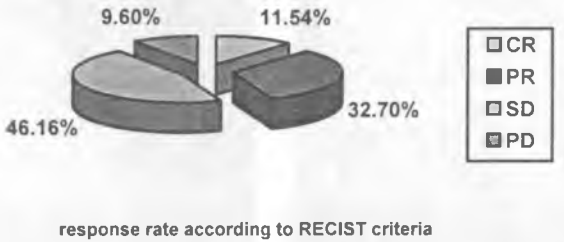

Fig. 6. Therapy response assessed according to RECIST (CR- complete response, PR – partial response, SD- stable disease, PD – progressive disease)

DISCUSSION

Neoadjuvant treatment of esophageal cancer prior to surgery was thought to improve survival by reduction of the primary tumor lesion as well as of regional and systemic tumor spread. However until now, prospective randomized trials could not prove the effectiveness of chemotherapy in terms of prolonged survival or higher rate of cure (3,6). Single-agent therapy response in this disease is modest (10 to 40%), combination therapy has been more promising, with response rates between 50% and 70% for cisplatin-based doublets (2). One advantage of preoperative chemotherapy for esophageal cancer is the possibility of downstaging the primary tumor and hence enhancing resectibility, allowing a more conservative surgical approach, and also potentially improving local control. Another advantage is the ability to assess response to preoperative chmotherapy directly in the primary tumor, making the end point of adjuvant therapy more precise by identifying those patients who respond to chemotherapy and who might therefore benefit from postoperative chemotherapy. The most important advantage however is that early administration of chemotherapy facilitates treatment of subclinical metastatic disease at a time when chemotherapy is likely to have its greatest impact (6,8,9). Preoperative chemotherapty treatment should result in better drug delivery to the tumor as the local blood supply has not been disturbed by operative dissection. Distant control should be enhanced as remote micrometastases are treated early without having to wait for postsurgical recovery (2). Though radiographic improvement can be seen in up to one half of patients, two or three cycles (6-12 weeks) of chemotherapy are required, relief of dysphasia is slow and/or incomplete, and survival is anecdotal. Unfortunately, there is no way to select "responders" prior to beginning therapy, leaving 50% of patients without a hope of benefit from therapy (2).

The drawback of early systemic therapy, in general include the theoretical possibility of a growth advantage for tumor cells undergoing spontaneous mutation into chemotherapy-resistant tumor cells and the possibility of a delay in achieving effective local tumor control, increasing the risk of tumor spread from the primary during preoperative chemotherapy (4,6,7,15,16).

The standard method for assessing the response of a tumor to treatment is to determine its change in maximum cross-sectional area. Using WHO criteria for tumor response goes as follows: • Complete response (CR) – complete disappearing of all known diseases; • Partial response (PR) – at least 50% reduction in tumor size; • No change – Stable disease (SD) – neither PR or PD; • Progression of the disease (PD) – greater than 25% increase in size of at least one lesion (or a new lesion) (1,5).

In an attempt to establish more accurate evaluation criteria in 1994 the European Organization for Research and Treatment in Oncology, the US National Cancer Institute and the National Cancer Institute of Canada introduced new guidelines, called: Respond Evaluation Criteria in Solid Tumors (RECIST). While WHO criteria evaluated the response to treatment by means of a bidimensional evaluation, defined by the maximum axial diameter of the lesion, the new guidelines require a uni-dimensional evaluation, defined by the maximum axial diameter of the lesion.

which is considered sufficient to assess the level of response to treatment. In RECIST the partial response is defined as a >30% decrease in the sum of the longest diameters of target lesions, progression is defined as a >20% increase in the sum of the longest diameters (Tab. 1) (1, 13, 14, 17).

Table 1. WHO and RECIST criteria for tumor response (14)

	WHO	RECIST
Measurability	Measurable, bidimensional Non-measurable/evaluable	Measurable, unidimensional: Conventional method – 20 mm; Spiral CT–10 mm; Target versus non-target lesion Non-measurable
Complete response (CR)	Disappearance of all known lesion(s); confirmed at 4 weeks	Disappearance of all known lesion(s); confirmed at 4 weeks
Partial response (PR)	At least 50% decrease; confirmed at 4 weeks	At least 30% decrease; confirmed at 4 weeks
Stable disease (SD)	Neither PR nor PD criteria met	Neither PR nor PD criteria met
Progressive disease (PD)	25% increase; no CR, PR or SD documented before increased disease, or new lesion(s)	20% increase; no CR, PR, or SD documented before increased disease, or new lesion(s)

Monitoring response of tumors to treatment is an integral and increasingly important function of radiologists working in oncological imaging. Imaging studies play a pivotal, objective role in quantifying tumor response to a variety of physical and pharmaceutical treatments. Standardized criteria for measuring therapeutic response were adopted in 1981 but have been modified by various cancer organizations. The RECIST criteria have been introduced to unify response assessment criteria, to define how to choose evaluable lesions and to enable the use of new imaging technologies (spiral CT and MRI) (17).

The RECIST documentation goes beyond lesion selection, measurement and assessment of response. It also makes specific recommendations on the usage of imaging techniques. The CT protocols are particularly detailed (imaging parameters for incremental and spiral machines, use of contrast enhancement and the presentation of images). The implications of this document are wide ranging and are likely to have cost and manpower implications for radiology departments in cancer treatment centers (13, 17).

The major proposed change is that RECIST uses one-dimensional measurements of the sum of the longest diameters (LDs) of tumors instead of the conventional bidimensional WHO method of the product of the longest diameter and that perpendicular to it, summed over all measured tumors. Also, the criteria for progressive disease (PD) differ between RECIST and WHO guidelines. The definition of complete response (CR) is essentially the same between the guidelines; however, the definition of partial response (PR) differs. For PR, WHO requires a 50% decrease in the sum of the products of the perpendicular diameters from baseline, confirmed at 4 weeks, whereas RECIST requires at least a 30% decrease in the sum of LDs from baseline, confirmed at 4 weeks. These criteria are almost equivalent if one assumes spherical tumors and that the LD and the diameter perpendicular to the LD both decrease by at least 30% (although the latter was not measured by RECIST) because then the sum of the products of the diameters would decrease by approximately 50% or more. The criteria for progressive disease (PD) also differ between the guidelines. WHO requires at least a 25% increase of one or more lesions (or the appearance of new lesions), whereas RECIST requires at least a 20% increase in the sum of LDs over the smallest sum subsequent to the start of treatment (or the appearance of new lesions) (5, 14).

Chemotherapy offers the treatment of distant foci of tumor. However the results from the use of chemotherapy as a single-line therapy have been disappointing. Both chemotherapy and radiation may be used as pre- or postoperative therapy (3).

CONCLUSIONS

CT enables precise assessment of esophageal carcinoma response to neoadjuvant chemotherapy. The WHO criteria of tumor response are the most widely used. The CT assessment provides the precise evaluation of the diameters of the tumor, and the presence of local and distal lymph node enlargement and metastases. RECIST criteria are comparable to those of WHO, but are more useful in spiral CT. The progression of the disease is found in smaller group of patients using RECIST criteria.

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SUMMARY

The aim of the study was presenting the use of CT in evaluating esophageal carcinoma response to neoadjuvant chemotherapy using WHO and RECIST guidelines. The material comprised a group of 47 men (aged 35–72 years) and 5 women (aged 40–54 years) with diagnosed esophag-

eal carcinoma. In all patients CT examination of the esophagus was performed, using CT scanner Somatom AR. T by Siemens, in 5 mm thick axial sections before and after administering contrast agent intravenously and orally. The control CT examination was performed in each patient after the proper course of neoadjuvant chemotherapy, using the same scanning protocol. Adenocarcinoma was found in 16 patients and squamouscell carcinoma in 36. Twenty-five patients were in clinical stage IIA, 5 patients in stage IIB and 22 patients was in stage III. The narrowing of the esophageal lumen was found in 51 patients, with dilatation above the narrowing in 30 of them. The thickness of the esophageal wall was between 5–25 mm. After chemotherapy the complete CT response was found in 6 patients (11.54%), and in 3 of them it was complete histopathological response. In 15 patients (28.85%) the partial response was found. In 21 patients there was no change after chemotherapy, and in 10 the progression was found. According to RECIST criteria total response was found in 6 patients, partial response in 17, and stable disease in 24 and progression in 5 of them. The assessment of the complete response was identical according to both WHO and RECIST guidelines. Only in assessment of the progressive diseases (PD) the differences were statistically significant ($p<0.05$). Local lymph node enlargement was found in 23 patients. In 4 of them there was enlargement of multiple lymph nodes. After chemotherapy the enlarged local lymph node were found in 17 patients. Conclusions: CT enables precise assessment of esophageal carcinoma response to neoadjuvant chemotherapy. The WHO criteria of tumor response are the most widely used. The CT assessment provides the precise evaluation of the diameters of the tumor, and the presence of local and distal lymph node enlargement and metastases. RECIST criteria are comparable to those of WHO, but are more useful in spiral CT. Spastically significant differences were found only in assessment of diseases progression.

Ocena TK stopnia odpowiedzi raka przełyku na chemioterapię przedoperacyjną według kryteriów WHO i RECIST

Celem pracy jest przedstawienie zastosowania TK w ocenie stopnia odpowiedzi na chemioterapię przedoperacyjną raka przełyku według kryteriów WHO i RECIST. Materiał obejmuje 47 mężczyzn i 5 kobiet z rakiem przełyku. U wszystkich pacjentów wykonano badanie TK przełyku przed i po przedoperacyjnej chemioterapii. Oceniano stopień odpowiedzi na leczenie przedoperacyjne według kryteriów WHO i RECIST. Wyniki poddano analizie statystycznej. Po chemioterapii całkowitą odpowiedź TK stwierdzono u 6 pacjentów (11,54%), a 3 z nich miało całkowitą odpowiedź histopatologiczną. U 15 pacjentów (28.85%) stwierdzono częściową odpowiedź. U 7 pacjentów stwierdzono odpowiedź minimalną, u 14 brak zmian po leczeniu. U 10 pacjentów stwierdzono progresję choroby. Według kryteriów RECIST całkowitą odpowiedź stwierdzono u 6 pacjentów, częściową u 17, stabilizację choroby u 24 i progresję u 5. Jedynie różnica w ocenie progresji choroby między kryteriami RECIST i WHO jest istotna statystycznie ($p<0,05$). TK umożliwia precyzyjną ocenę stopnia zaawansowania raka przełyku oraz ocenę stopnia odpowiedzi na przedoperacyjną chemioterapię. Kryteria WHO stopnia odpowiedzi guza na leczenie są stosowane powszechnie. Kryteria RECIST są porównywalne z kryteriami WHO i są bardziej użyteczne dla spiralnej tomografii komputerowej. Istotna statystycznie jest jedynie różnica w ocenie progresji choroby, która jest stwierdzana u mniejszej liczby pacjentów niż według WHO.