The value of magnetic resonance imaging in the assessment of chemoradiotherapy of cancer of cervix uteri

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ABSTRACT

Background and aim. Magnetic resonance imaging (MRI) is one of the most useful and frequent methods of examinations to monitor patients after chemoradiotherapy, in order to assess residual tumor tissue and relapse of the disease. This study aims to evaluate the diagnostic value of MRI in the assessment of the effectiveness of the treatment of cancer of cervix uteri.

Materials and methods. Retrospective data of 52 patients were obtained. All these patients underwent pelvic MRI in the Hospital of Lithuanian University of Health Sciences Kauno klinikos to assess the malignant tumor of cervix six months after chemoradiotherapy in the year 2010. MRI diagnostic value characteristics were calculated, compared with clinical data, obtained in the period of 5 or more years after chemoradiotherapy.

Results. Residual tumor tissue was found in 25.0 % of patients. In 28.2 % of patients with non-keratinizing squamous cell carcinoma, in 20.0 % of patients with keratinizing squamous cell carcinoma and 0.0 % of patients with adenocarcinoma, the residual tumor was found. In 100 % of patients with G1 tumors, in 23.4 % of patients with G2 tumors and 25.0 % of patients with G3 tumors, residual tumor tissue was found. In 12.5 % of cases the residual tumor was diagnosed within the range of 1.0-3.0 cm, in 19.2 % – within the range of 3.0-5.0 cm, in 25.0 % – within the range of 5.0-7.0 cm, in 75.0 % – within the range of 7.0-9.0 cm, in 75.0 % – within the range of 7.0-9.0 cm. In 26.5 % of patients with tumor extension to parametrium, in 28.6 % of patients with tumor extension to corpus uteri/vagina, in 60.0 % of patients with tumor extension to bladder/rectum and 28.1 % of patients with abnormal pelvic lymph nodes, residual tumor tissue was found. The specificity of MRI in the detection of residual tumor was 100.0%, sensitivity – 63.6%, positive prognostic value (PPV) – 100.0%, negative prognostic value (NPV) – 78.9% and accuracy – 84.6%. Matthews correlation coefficient (MCC) was 0.71.

Conclusions. MRI allowed diagnosing residual tumor tissue in 25.0 % of patients. Residual tumor tissue was most commonly diagnosed in patients with non-keratinizing squamous cell carcinoma, G1 carcinoma, large tumors and tumors with invasion to bladder and rectum. In the diagnostic of residual tumor tissue, MRI showed moderate sensitivity, high specificity, accuracy, PPV and NPV.

Keywords: magnetic resonance imaging, cancer of cervix uteri, chemoradiotherapy, residual tumor tissue.

INTRODUCTION

Cancer of cervix uteri is the second most frequent cancer and the third cause of death in the world [1–3]. Disease relapses and causes death in approximately 30 % of female patients. According to the literature data, 5-years survival is only 64 % [3, 4].

According to the data presented by the National Cancer Institute, in 2012 the incidence of cancer of cervix uteri in all age groups accounted for 5 % of all malignant tumors in females. The incidence of the cancer of cervix uteri in females in the age group of 15-29 years was the second after the incidence of thyroid cancer and accounted for 13 % of all cancers. In 2012, mortality from cancer of cervix uteri in Lithuania in all age groups accounted for 6 % of all malignant tumors. Mortality from cancer of cervix uteri in the age group of 35-54 years was the second after mortality from breast cancer and accounted for 15 % [5].

Accurate assessment of the extent of the spread of cancer is extremely important for the selection of the appropriate treatment modality. However, the medical examination does not allow identification of the size of a tumor, especially when infiltrative tumors are diagnosed and tumor in-

filtrates parametrium and pelvic wall and when lymph node metastases are observed. A biopsy may not agree with the results of postoperative histopathological examination because tumors are often heterogenic. Non-invasive visualization methods provide useful additional information which is necessary for precise evaluation of the clinical stage [6].

The prognosis of the disease depends on the stage at the time of diagnosis, the size of the tumor, its histological type, stromal infiltration, local and distant metastases [6]. Magnetic resonance imaging (MRI) is extremely valuable for the evaluation of the local extent of cancer of cervix uteri which predetermines the selection of treatment modality and prognosis of the disease. MRI is especially valuable in patients selected for chemoradiotherapy when radical hysterectomy is impossible [2, 7].

It is essential to monitor patients after chemoradiotherapy in order to assess residual tumor tissue and relapse of the disease. In this case, clinical examination is not very accurate. Computed tomography (CT) does not allow precisely to differentiate residual tumor tissue with radiation fibrosis and other possible abnormalities, and therefore MRI is one of the most useful and frequent methods of examinations. When a residual tumor is detected, and additional chemotherapy and radiotherapy are applied survival prognosis improves, and therefore, early diagnosis of relapse or residual tumor is of extreme value [8, 9].

AIM

To evaluate the diagnostic value of MRI in the assessment of the effectiveness of the treatment of cancer of cervix uteri.

OBJECTIVES

1. To determine the number of patients with residual tumor tissue detected by the MRI method.
2. To assess the distribution of residual tumor tissue according to the size of the previous tumor, local extension, histological type and grade of differentiation.
3. To calculate the sensitivity of MRI, its specificity, accuracy, positive prognostic value (PPV), negative prognostic value (NPV) in the evaluation of the effectiveness of treatment.

MATERIALS AND METHODS

Retrospective data of 52 (n=52) patients were obtained from the Registration Office of the Department of Obstetrics and Gynaecology of the Hospital of Lithuanian University of Health Sciences Kauno klinikos archive and Hospital Information System (HIS). All these patients underwent pelvic MRI in the Department of Radiology to assess the malignant tumor of cervix six months after chemoradiotherapy in the year 2010.

Pelvic MRIs were performed by 1.5 T MRI scanner "Siemens Magnetom Avanto Syngo MR B 15", equipped with a pelvic coil, with patients in a supine position, their hands raised overhead, and legs straighten. Anterior, lateral, axial and axial oblique plains were employed according to pelvic examination protocol.

The first phase involved a native scan in T1W/TIRM, T1W/TSE, and T2W/TSE sequences. The second stage included a DW/EPI sequence using b values of 50, 400 and 800 s/mm2. ADC maps were reconstructed from DW images. The third phase consisted of T1W/TSE and T1W/SE/FS sequences using an intravenous gadolinium-based contrast medium. Contrast medium was injected into a peripheral vein; the precise amount was calculated according to the patient's body weight: 1 ml product / 5 kg body weight or 15 ml / 75 kg.

The following patients' characteristics were used for the research data analysis: patients' age, tumor size and extent before treatment, histological type, and differentiation grade. Tumor size and extent were assessed using MRI data obtained before chemoradiotherapy. Assessment of tumor histological type and differentiation grade were based on data of morphological examination of biopsy specimens obtained before initiation of treatment. The number of cases with residual tumor detected using MRI 6 months after chemoradiotherapy was also assessed. MRI sensitivity, specificity, and accuracy were also calculated as well as PPV and NPV compared with clinical data obtained in the period of 5 or more years after chemoradiotherapy.

According to various authors, a 5-years survival period after the treatment of cancer of cervix uteri was selected because a statistically signifi-

cant decrease in a number of relapses after that period is observed and follow-up visits are required only once yearly. This period is sufficient to determine the absence of relapse or residual tumor tissue as weighted regression [10].

The Matthews correlation was used to identify classification quality.

The obtained data were analyzed using software packages "SPSS 17.0" and "Excel 2016". The selected level of statistical significance was $p < 0.05$. Quantitative data were presented as an average and a standard deviation. Qualitative data were presented as absolute numbers and percentages.

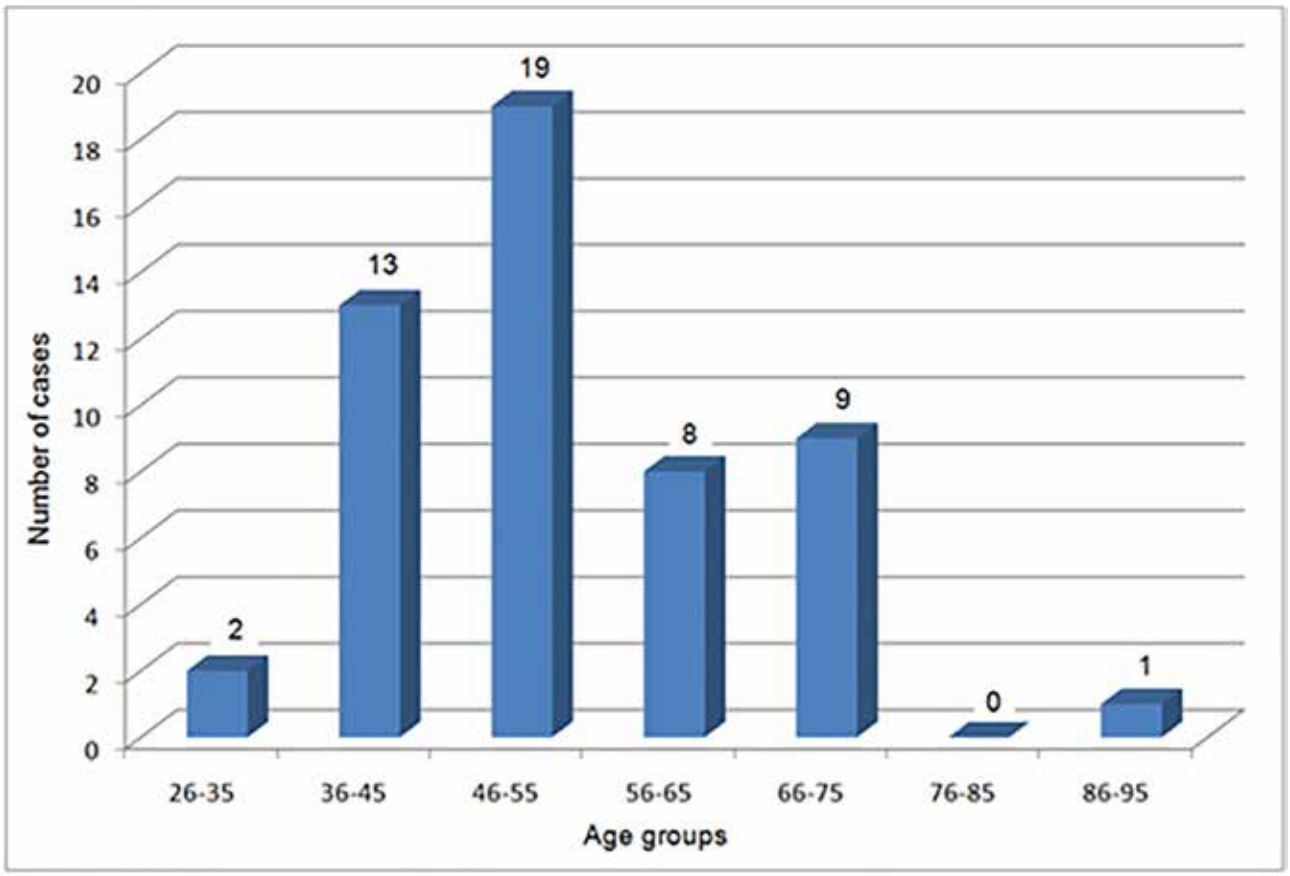
RESULTS

In 2010 in the Clinic of Radiology MRI to assess the tumor of cervix uteri six months after chemoradiotherapy was performed in 52 patients. Patients' age ranged from 29 to 86 years, the average age was 52.9 11.86 years (Figure 1). Histological examination showed keratinizing squamous cell carcinoma in 39 patients (75.0 %), non-keratinizing squamous cell carcinoma in 10 patients (19.2 %) and adenocarcinomas in 3 patients (5.8 %).

In 1 patient (1.9 %) G1 grade was established at diagnosis, in 47 patients (90.4 %) – G2 grade, and in 4 patients (7.7 %) – G3 grade.

Tumor distribution by tumor sizes was assessed, it ranged from 1.2 to 11.0 cm, average was 4.74±1.90 cm. 8 number of cases (15.4 %) were within 1.0 – 3.0 cm, 26 (50.0 %) – within 3.0 – 5.0 cm, 12 (23.1 %) – within 5.0 – 7.0 cm, 4 (7.7 %) – within 7.0 – 9.0 cm, 2 (3.8 %) – within 9.0 – 11.0 cm range.

Figure 1. Patients' distribution by age groups



The local extension of the tumor was assessed. Invasion to parametrium was diagnosed in 49 patients (94.2 %), invasion to corpus uteri/vagina was diagnosed in 28 patients (53.8 %) and invasion to bladder/rectum was diagnosed in 5 patients (9.6 %).

MRI performed six months after chemoradiotherapy was used to assess the number of patients with residual tumor; it was diagnosed in 13 patients (25.0 %) (Figure 2).

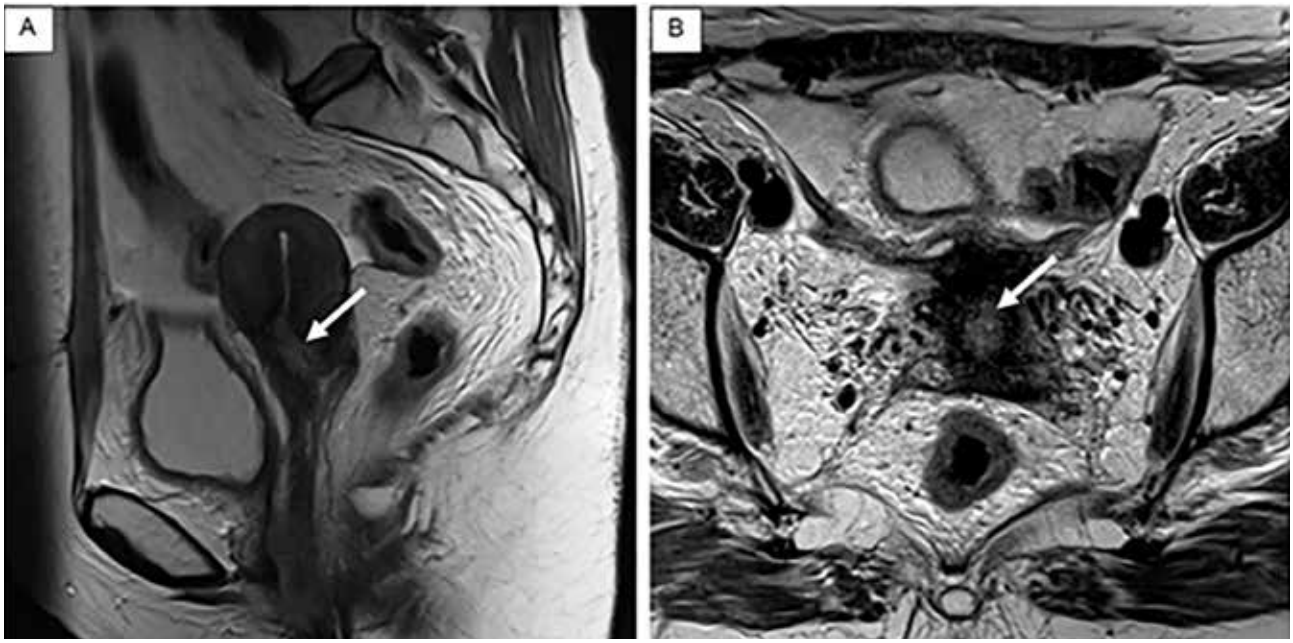


Figure 2. Pelvic MRI, T2W/TSE sequence, lateral (A) and axial (B) planes. Cervix uteri are large; its structure is heterogeneous – changes after chemoradiotherapy. Infiltration with abnormal SI is observed along the cervical canal – residual tumor masses

Residual tumor tissue was not found in 39 patients (75.0 %) (Figure 3).

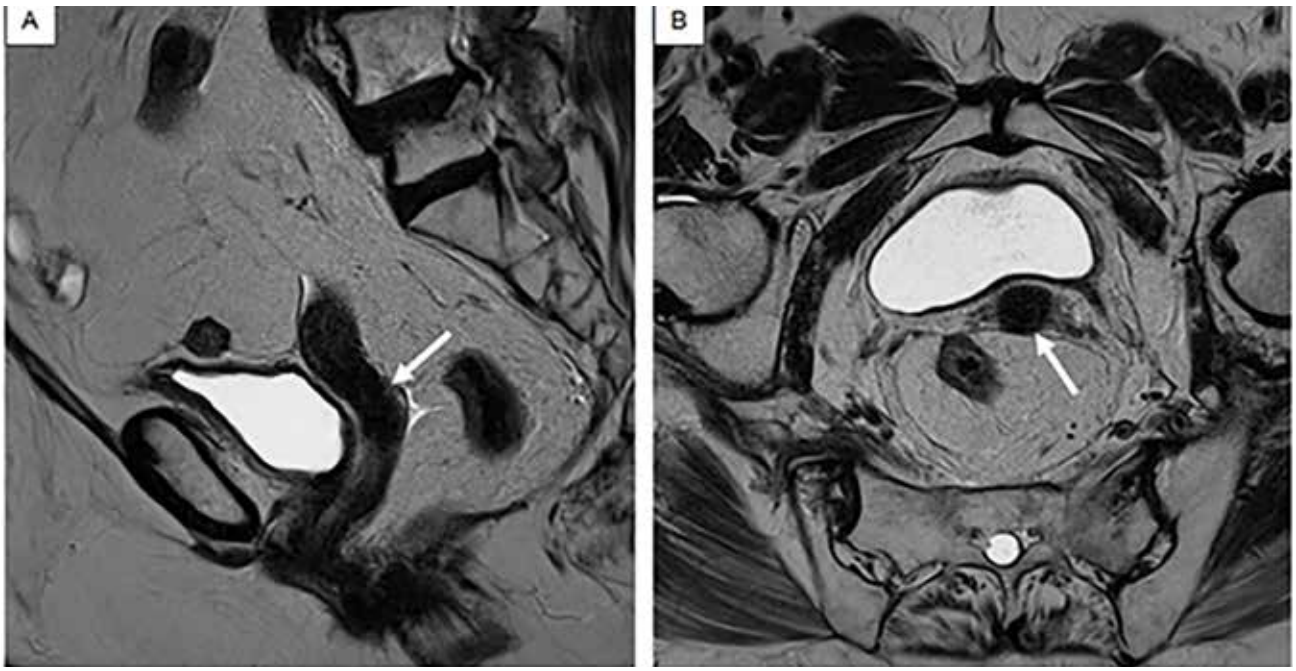
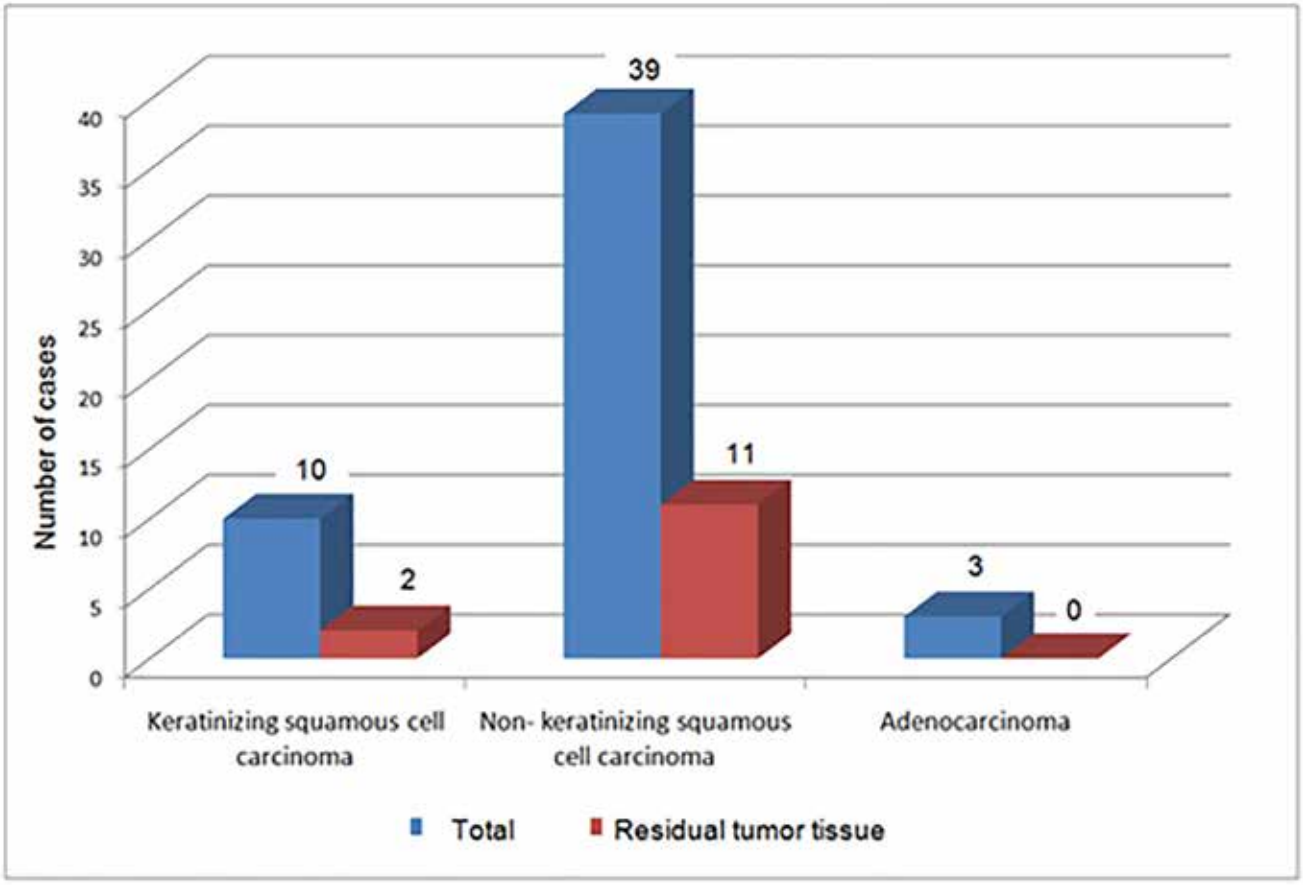


Figure 3. Pelvic MRI, T2W/TSE sequence, lateral (A) and axial (B) planes. Changes after chemoradiotherapy are visible. Cervix uteri are small in size, homogeneous; no unusual SI lesions are observed (arrows).

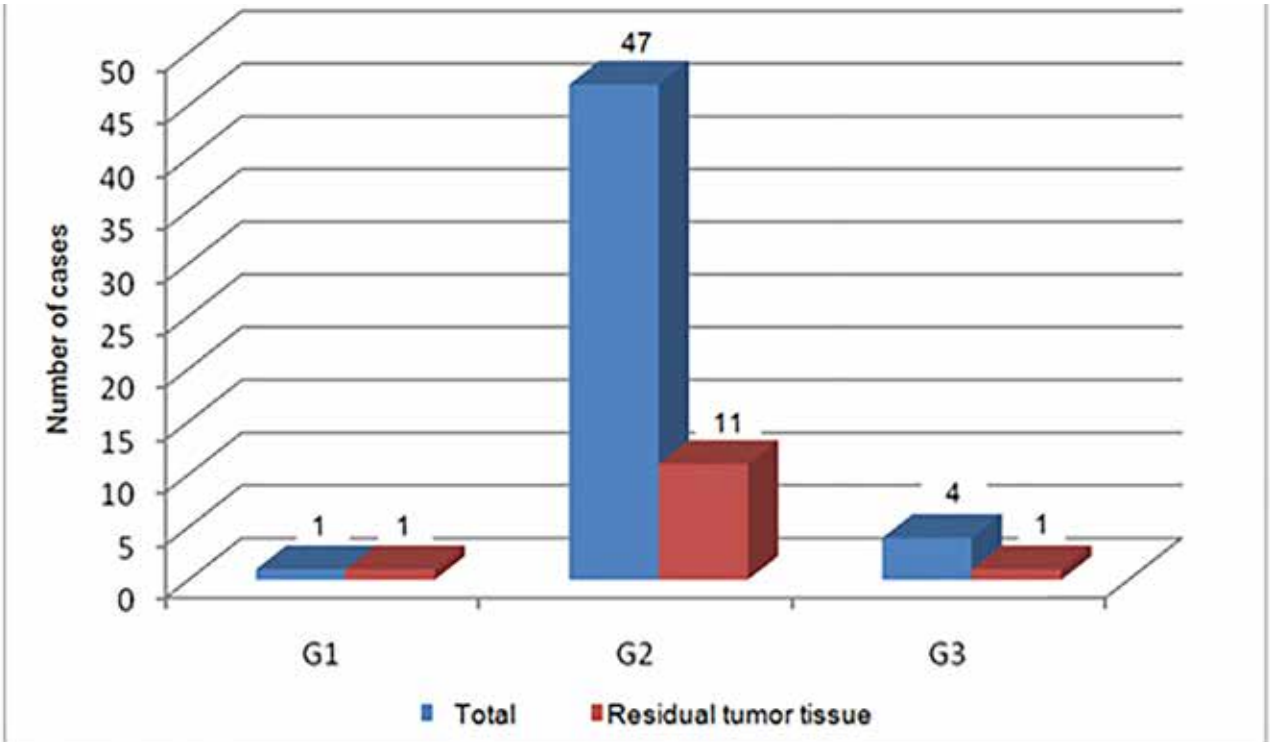
The distribution of residual tumor tissue by tumor histological type was analyzed. In 11 out of 39 patients (28.2 %) with non-keratinizing squamous cell carcinoma, residual tumor was found. In 2 out of 10 patients (20.0 %) with keratinizing squamous cell carcinoma, the residual tumor was found. Moreover, in 0 out of 3 patients with residual adenocarcinoma tumor was found (0.0 %) (Figure 4).

Figure 4. Residual tumor tissue distribution by histological type



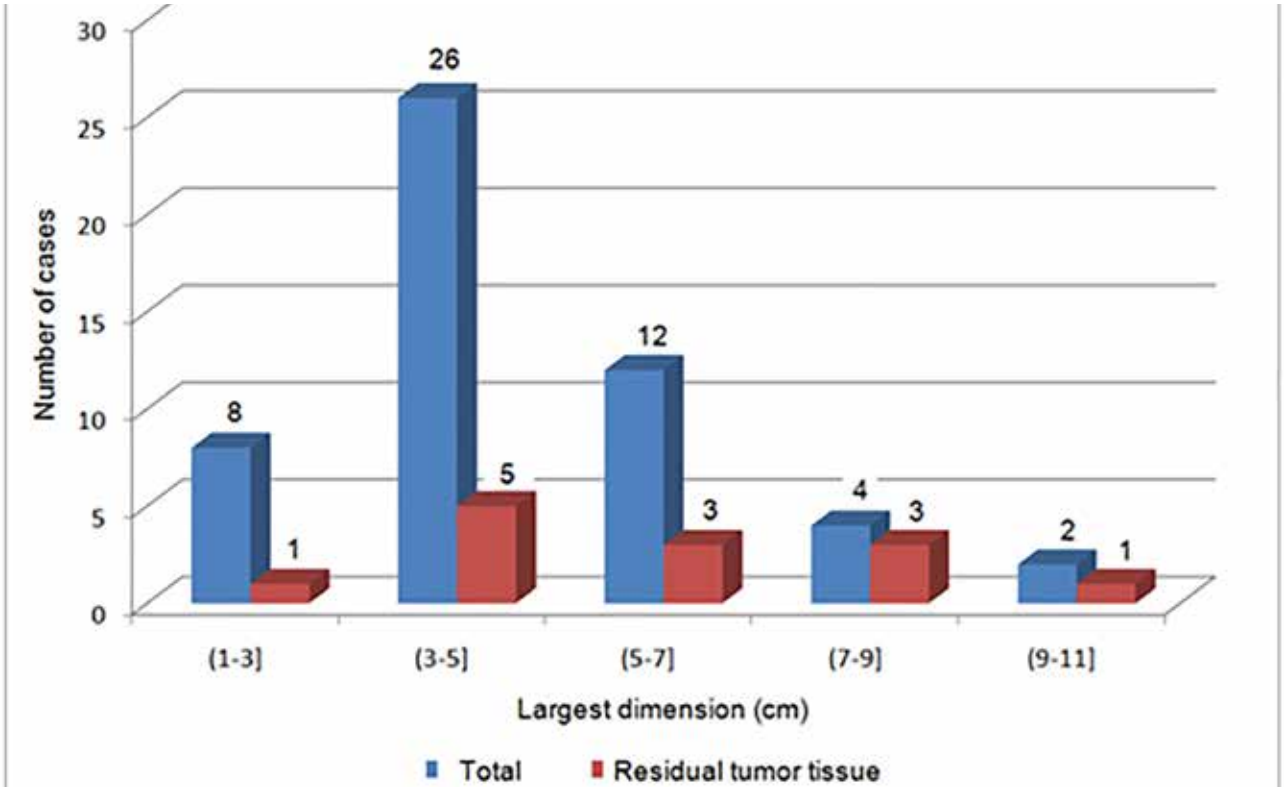
The distribution of residual tumor tissue by tumor differentiation grade was presented. In 1 out of 1 (100 %) patient with a G1 tumor, residual tumor tissue was found. In 11 out of 47 (23.4 %) patients with a G2 tumor, residual tumor tissue was found. Moreover, in 1 patient out of 4 (25.0 %) with a G3 tumor, residual tumor tissue was found (Figure 5).

Figure 5. Residual tumor tissue distribution by tumor grade



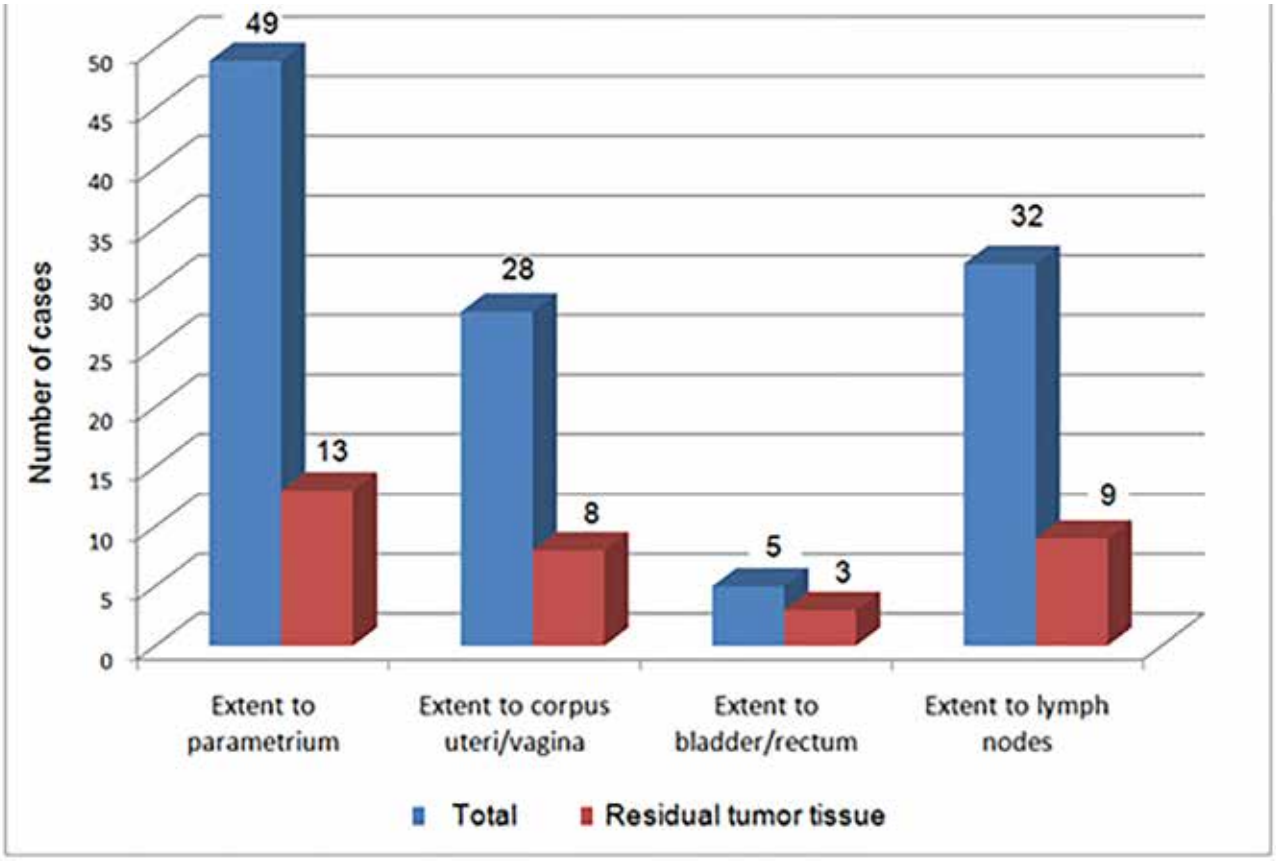
The number of cases with residual tumor tissue before treatment was compared with the tumor size (largest dimension). 1 out of 8 (12.5 %) residual tumor was diagnosed within the range of 1.0-3.0 cm. 5 out of 26 (19.2 %) residual tumor was diagnosed within the range of 3.0-5.0 cm. 3 out of 12 (25.0 %) residual tumor was diagnosed within the range of 5.0-7.0 cm. 3 out of 4 (75.0 %) residual tumor was diagnosed within the range of 7.0-9.0 cm. 1 out of 4 (75.0 %) residual tumor was diagnosed within the range of 7.0-9.0 cm (Figure 6).

Figure 6. Residual tumor tissue distribution by tumor size



The number of patients with residual tumor tissue was compared with local tumor extension before treatment. Extension to parametrium was diagnosed in 49 patients, 13 (26.5 %) of them were diagnosed with residual tumor tissue. Extension to corpus uteri/vagina was diagnosed in 28 patients, 8 (28.6 %) of them were diagnosed with residual tumor tissue. Extension to bladder/rectum was diagnosed in 5 patients, 3 (60.0 %) of them were diagnosed with residual tumor tissue. Abnormal pelvic lymph nodes were diagnosed in 32 patients, 9 (28.1 %) of them were diagnosed with residual tumor tissue (Figure 7).

Figure 7. Residual tumor tissue distribution by tumor extent



MRI was performed six months after chemoradiotherapy diagnostic value characteristics were calculated and compared with clinical data obtained after 5 or more years after chemoradiotherapy. MRI showed no tumor relapse in 38 patients. In 30 of them findings were real negative (TN) (MRI shows no residual tumor, and no clinical symptoms of the disease are observed within 5 years after chemoradiotherapy) and in 8 patients findings were false negative (FN) (MRI shows no residual tumor. However, disease relapses within 5 years after chemoradiotherapy). In 14 patients MRI showed residual tumor tissue, of them in 14 patients findings were real positive (TP) (MRI shows residual tumor tissue and disease relapses within five years after chemoradiotherapy). No false negative findings (FN) were obtained (MRI shows residual tumor tissue although no clinical signs of the disease are observed within five years after chemoradiotherapy) (Table 1).

Table 1. Outline of the calculation of MRI diagnostic value characteristics

Tests	Clinically confirmed	Clinically not confirmed
MRI diagnosed	14 (TP)	0 (FP)
MRI not diagnosed	8 (TN)	30 (FN)

According to the results obtained, diagnostic value characteristics of MRI performed six months after chemoradiotherapy were calculated: specificity – 100.0%, sensitivity – 63.6%, PPV – 100.0%, NPV – 78.9% and accuracy – 84.6%. Because no false positive finding was obtained, specificity and PPV were ideal.
Our research showed extremely high Matthews correlation coefficient (MCC=0.71). It shows the high quality of MRI diagnostic value characteristics.

DISCUSSION

In Lithuania and globally, cancer of cervix uteri is one of the most common malignancies in females. According to the data presented by the National Cancer Institute, it is most frequently diagnosed in females in 50-54 years age group [5]. According to the data of our research, it was most frequently diagnosed in females of 46-55 years age group. Therefore our results are close to the literature data.
Assessment of histological findings showed that squamous cell carcinoma is the most common in patients with cancer of cervix uteri. Adenocarcinoma is far rarer, and it accounts for 5-20 % of all cases of cancer of cervix uteri [11, 12]. Our research data are quite similar: squamous cell carcinoma (both keratinizing and non-keratinizing) was diagnosed in 49 out of 52 patients (94.2 %), and adenocarcinoma was diagnosed only in 3 out of 52 patients (5.8 % of all cases).
According to the data of the study conducted by G. Somoye et al., the disease relapses in 30 % of patients, and 5-years survival is approximately 64 % [4]. According to the study of Attia M. A. et al., local relapse after chemoradiotherapy was diagnosed in 31.2 % of patients [13]. According to many authors, the disease relapses in 35-61 % of patients [14]. Our research data show that residual tumor tissue is found slightly more rarely by MRI performed six months after chemoradiotherapy and made up 25 % of all examined patients.
According to multiple studies, the comparison of relapse number and its previous size shows that the tumor size is a significant prognostic factor. The study of Werner-Wasik et al., showed that in patients with more substantial than 5cm tumor size, relapse was diagnosed in 83 % of patients if compared to the number of relapses in patients with the tumor smaller than 5 cm (53 %). In patients with FIGO stages I and II, the tumor size is even more critical prognostic factor if compared to the stage of the disease [15]. Our study also showed that the majority of patients with residual tumor tissue were diagnosed in the group of patients with large tumor (5-7 cm), ant its accounted for 75.0 % of all cases.
Extension to parametrium significantly increases the risk of the residual tumor tissue. According to the study of Werner-Wasik et al., the tumor relapse was diagnosed in 25 % of patients that were not diagnosed with tumor extension to parametrium at initial examination and in 54 % of patients with diagnosed tumor extent to parametrium [15]. Our research showed better results – residual tumor tissue was diagnosed in 26.5 % of patients with tumor extension to parametrium.
Literature presents insufficient data concerning the tumor differentiation impact on residual tumor tissue and tumor relapse. Several studies showed that the tumor differentiation grade has no significant effect on the development of tumor relapse [16, 17]. We had only one patient with G1 grade and four patients with G3, so it is impossible to make a relevant conclusion concerning the grade of differentiation and residual tumor tissue.
Several studies were conducted to assess the character of the diagnostic value of MRI in the tumor relapse and residual tumor tissue diagnostic. Many studies evaluated MRI sensitivity

and specificity in the diagnosis of tumor relapse after chemoradiotherapy. E. Vincens et al. conducted one of the most extensive studies. They assessed 43 MRIs after chemoradiotherapy and found that MRI sensitivity was 80 % and specificity was 55 %. There were 50 % of FN findings and 17 % of FP findings [18]. In the study conducted by P. Lavoue et al. 29 MRIs performed after chemoradiotherapy were assessed. MRI sensitivity was 77 %, and specificity was 60 % [14]. According to the data presented by H. Hricak et al., MRI accuracy in assessing the tumor relapse after chemoradiotherapy was 78 %, PPV – 65 % and NPV – 97 %. The accuracy of MRI, conducted earlier than six months after radiotherapy was 69% and specificity was 46 %. These diagnostic value characteristics were much higher when MRIs were conducted in more than six months after initiation of chemoradiotherapy: accuracy was 88 %, and specificity was 81 % [19]. Therefore, our research shows that MRI is considerably more accurate and sensitive when it is conducted not earlier than six months after treatment. MRIs that we have assessed were conducted six months after chemoradiotherapy. Our accuracy was somewhat similar, and it was 86.6 %, and specificity was 100 %.

Due to insufficient sample size during our research, we did not calculate the correlation between residual tumor tissue and histological type, grade of differentiation and tumor local extent.

CONCLUSIONS

1. MRI allowed diagnosing residual tumor tissue in 25.0 % of patients. Moreover, residual tumor tissue was not found in 75.0 % of patients.
2. Patients with non-keratinizing squamous cell carcinoma and well-differentiated carcinoma of cervix uteri were most commonly diagnosed with residual tumor tissue.
3. Residual tumor tissue was most commonly diagnosed in patients with large (7.0-9.0 cm) tumors and patients with tumor invasion to bladder and rectum.
4. In the diagnostic of residual tumor tissue, MRI showed moderate sensitivity, high specificity, accuracy, PPV and NPV.

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