Magnetic resonance imaging in the evaluation of standard radiotherapy field borders in patients with uterine cervix cancer*

Ressonância magnética para avaliação dos limites dos campos clássicos de radioterapia em pacientes portadoras de neoplasia maligna de colo uterino

Geison Moreira Freire[1], Rodrigo Souza Dias[2], Adelmo José Giordani[3], Julisa Chamorro Lascasas Ribalta[4], Helena Regina Comodo Segreto[5], Roberto Araujo Segreto[6]

Abstract **OBJECTIVE: To evaluate, by means of magnetic resonance imaging, the standardized field borders in radiotherapy for malignant neoplasm of uterine cervix, and to determine the role of this method in the reduction of possible planning errors related to the conventional technique. MATERIALS AND METHODS: Magnetic resonance imaging studies for planning of treatment of 51 patients with uterine cervix cancer were retrospectively analyzed. The parameters assessed were the anterior and posterior field borders on sagittal section. RESULTS: The anterior field border was inappropriate in 20 (39.2%) patients and geographic miss was observed in 37.3% of cases in the posterior border. The inappropriateness of both field borders did not correlate with clinical parameters such as patients' age, tumor staging, histological type and degree. CONCLUSION: The evaluation of standardized field borders with the use of magnetic resonance imaging has demonstrated high indices of inappropriateness of the lateral field borders, as well as the relevant role of magnetic resonance imaging in the radiotherapy planning for patients with uterine cervix cancer with a view to reduce the occurrence of geographic miss of the target volume.**

Keywords: Uterine cervix cancer; Radiotherapy planning; Magnetic resonance imaging; Geographic miss; Tumor volume.

Resumo **OBJETIVO: Avaliar os limites de campo padronizados para radioterapia de neoplasia maligna de colo uterino com o uso de ressonância magnética e verificar a importância deste exame na redução de possíveis erros de planejamento com técnica convencional. MATERIAIS E MÉTODOS: Foram analisados, retrospectivamente, exames de ressonância magnética do planejamento de 51 pacientes tratadas devido a neoplasia de colo uterino. Os parâmetros estudados foram limites anterior e posterior no corte sagital. RESULTADOS: Observou-se, no corte sagital das ressonâncias magnéticas, que o limite de campo anterior apresentou-se inadequado em 20 (39,2%) pacientes e que houve perda geográfica em 37,3% dos casos no limite posterior. A inadequação de ambos os limites de campo não se relacionou com parâmetros clínicos como idade das pacientes, estadiamento, tipo e grau histológico. CONCLUSÃO: A avaliação dos limites de campo padronizados pela literatura com o uso de ressonância magnética mostrou altos índices de inadequação dos limites do campo lateral, assim como a importância do uso deste exame no planejamento radioterápico de pacientes portadoras de câncer de colo uterino com a finalidade de reduzir a perda geográfica no volume alvo de tratamento.**

Unitermos: Câncer de colo uterino; Radioterapia; Imagem por ressonância magnética; Perda geográfica; Volume tumoral.

Freire GM, Dias RS, Giordani AJ, Ribalta JCL, Segreto HRC, Segreto RA. Magnetic resonance imaging in the evaluation of standard radiotherapy field borders in patients with uterine cervix cancer. Radiol Bras. 2010;43(3):175–178.

INTRODUCTION

Uterine cervix cancer is the second most frequent neoplasm among women. Most of these patients are found in developing countries and, in some of them, this is the type of cancer with highest incidence in the female population[1]. The Brazilian Cancer Institute (Instituto Nacional de Câncer – INCA) has estimated the occurrence of 18,430 new cases of this disease in 2010, with an estimated risk of 18 cases in every 100,000 women[2].

Radiotherapy plays a significant role as a therapeutic strategy for this disease, with curative or even palliative purposes. Two

* Study developed at the Unit of Radiotherapy – Universidade Federal de São Paulo (Unifesp), São Paulo, SP, Brazil.

1. Fellow Master degree, Unit of Radiotherapy – Universidade Federal de São Paulo (Unifesp), São Paulo, SP, Brazil.

2. Master, Physician Assistant, Unit of Radiotherapy – Universidade Federal de São Paulo (Unifesp), São Paulo, SP, Brazil.

3. PhD, Physicist, Unit of Radiotherapy – Universidade Federal de São Paulo (Unifesp), São Paulo, SP, Brazil.

4. Private Docent, Associate Professor, Department of Gynecology – Universidade Federal de São Paulo (Unifesp), São Paulo, SP, Brazil.

5. Post-doctorate degree, Associate Professor, Unit of Radiotherapy – Universidade Federal de São Paulo (Unifesp), São Paulo, SP, Brazil.

6. Private Docent, Associate Professor and Head for the Unit of Radiotherapy – Universidade Federal de São Paulo (Unifesp), São Paulo, SP, Brazil.

Mailing address: Dr. Roberto Araujo Segreto. Rua Pascal, 778, ap. 102, Campo Belo. São Paulo, SP, Brazil, 04616-002. E-mail: segreto.dmed@epm.br

Received October 2, 2009. Accepted after revision April 16, 2010.

radiotherapy modalities are employed in the management of this tumor, namely, teletherapy and brachytherapy. Teletherapy is a technique where the radiation source is distant from the target lesion, and is utilized in the treatment of the whole pelvis, including the lesion, uterus, vagina, parametrium and the regional lymphatic system. In brachytherapy, the radiation source is placed in direct contact with the target volume to be treated[3–5].

In teletherapy, the most frequently utilized technique includes four radiotherapy fields, namely, one anterior field, another posterior, and two latero-lateral fields, covering the whole target volume to be treated[6].

Besides the staging methods recommended by International Federation of Gynecology and Obstetrics (FIGO), magnetic resonance imaging (MRI) is a valuable method for women with this disease, since it allows the delineation of the typical female pelvic anatomy and mainly the evaluation of the local tumor extent[7,8].

The present study was aimed at evaluating the standard radiotherapy field borders by means of MRI in cases of uterine cervix cancer, , and to determine the role of this method in the reduction of possible planning errors related to the conventional technique.

MATERIALS AND METHODS

Before undergoing radiotherapy, 51 patients were staged according to the FIGO criteria and submitted to radiotherapy planning with orthogonal radiography and simulation of treatment fields, defining field borders based on bone references standardized by the literature.

Inclusion criteria were the following: patients aged ≥ 21 years, anatomopathologically confirmed diagnosis of uterine cervix neoplasm, patients with clinical stages IB to IVA (FIGO) and patients submitted to pretreatment MRI. Exclusion criteria were the following: contraindication for MRI, patients previously submitted to therapy and presence of another concomitant or previously treated pelvic neoplasm.

In the classical radiotherapy planning, the following parameters are utilized as limits for the anterior and posterior fields: the transition between the fourth and fifth lumbar vertebrae, the lower border of the obturator foramen or pubis, depending on the vaginal involvement, and laterally, at 1.5 cm from the small pelvis margin. For the lateral fields, the anterior border (AB) is the pubic symphysis, and the posterior border (PB) is the transition between the second and third sacral vertebrae (S2-S3) or including the whole vertebra S3[4]. All the patients underwent pelvic MRI before initiating the treatment. Sagittal T1- and T2-weighted sequences were performed in a Philips 1.0 tesla equipment.

With the assistance of a radiologist, the treatment volumes were delineated on MRI studies, considering the tumor and the uterine body as target volume, and the section demonstrating the volume with the largest anteroposterior diameter was selected. The MRI studies were retrospectively analyzed as regards the inclusion of the target volume in the standard radiotherapy fields. The following parameters were evaluated: anterior and posterior borders on the sagittal section at the level of the median line. A 1.0 cm safety margin around the tumor and the uterine body was adopted.

The data obtained in the present study were submitted to statistical analysis. Logistic regression was the inferential analysis employed to either confirm or reject the evidences observed in the descriptive analysis. The significance level for null hypothesis rejection was $p \leq 0.05$.

Clinical data of the patients, such as age, histological type, grade, and FIGO staging are shown on Table 1.

RESULTS

The evaluation of the appropriateness of radiotherapy field borders on sagittal MRI sections demonstrated inappropriate AB in 20 (39.2%) of the patients, and geographic miss in PB in 37.3% of cases (Figure 1).

No relation was observed between lateral field AB inappropriateness and clinical parameters such as patient's age (p = 0.970), tumor staging ($p > 0.999$), type (p = 0.162) and histological grade (p = 0.884). Also, the PB inappropriateness was not related with the clinical parameters, age (p = 0.726), tumor staging ($p > 0.999$), type (p = 0.496) and histological grade (p = 0.813).

As regards staging, a high rate of inappropriateness was observed in stages IIB (AB, 37.9% and PB, 34.4%) and IIIB (AB,

Table 1 Clinical characteristics of patients in the study sample.

Sample characteristics		*n*	Rate
Age (median in years)	54	–	–
Histological type	Spinocellular carcinoma	45	88.2%
	Adenocarcinoma	6	11.8%
Histological grade	X*	10	19.6%
	1	3	5.9%
	2	25	49.0%
	3	13	25.5%
Staging (FIGO)	IB	3	5.9%
	IIB	29	56.9%
	IIIB	15	29.4%
	IVA	4	7.8%

* Grade X: Histological grade not reported by the pathologist.

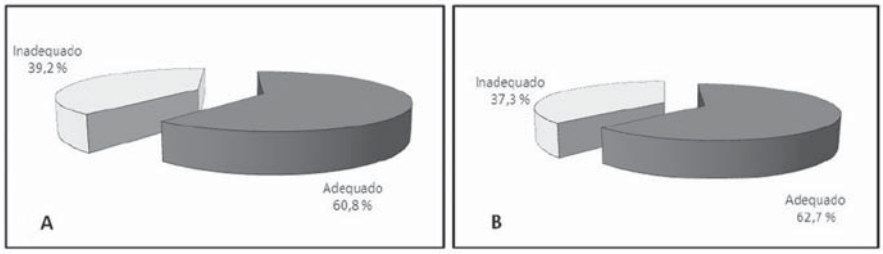

Figure 1. Distribution of individuals according to the appropriateness of anterior borders (**A**) and posterior borders (**B**) of lateral fields.

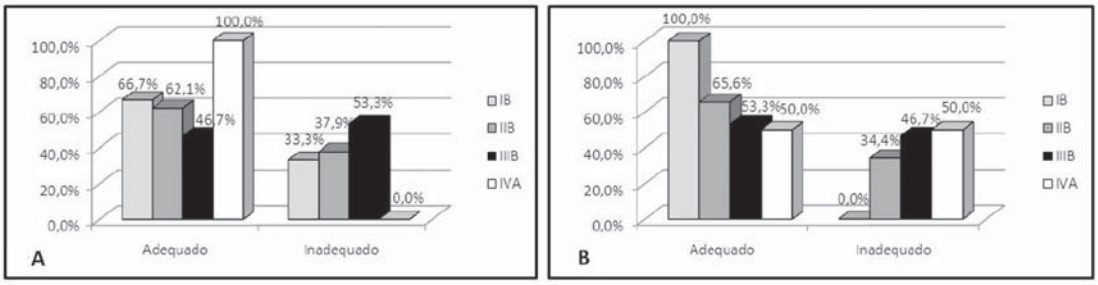

Figure 2. Distribution of individuals staging, according to the appropriateness of anterior borders (**A**) and posterior borders (**B**) of lateral fields (by staging).

53.3% and PB, 46.6%), as the patients at each specific stage were analyzed. Such results demonstrate that no statistical significance was observed in relation to the evaluated parameters and, consequently, errors may occur with any staging or histological grade (Figure 2).

In the analysis of the appropriateness of each histological grade, inappropriateness was observed in 33.3% (AB) in histological grade 1, 36% (AB) and 40% (PB) in grade 2, and 46.2% (PB) in grade 3, also demonstrating a greater planning error in higher histological grades.

DISCUSSION

Radiotherapy is the main therapeutic modality for locally advanced uterine cervix tumors, and the radiotherapy planning is essential for guaranteeing the treatment appropriateness. Classically, bone references were employed to define standard radiotherapy field borders, without considering the tumor characteristics and the patient's individual data. In the present study, the anterior and posterior borders of the lateral field were analyzed by means of MRI to evaluate the planned radiotherapy fields appropriateness.

The present study results regarding patients' characteristics show a median age at the diagnosis of 54 years (22 to 77 years), with predominance of spinocellular carcinoma in 88.2% of cases and locally advanced staging in 94.1%. This histological type of tumor is reported in the literature as the most frequent one[9–11]. There was a predominance of the most undifferentiated tumors with histological grades 2 (49%) and 3 (25.5%). The median age observed was similar to the ones found in other studies including patients with the same disease[9,11]. Thus the present results corroborate the literature, except for those related to predominant histological grades, since studies evaluating the utilization of MRI in radiotherapy planning have not taken this parameter into consideration[7,12,13].

As the appropriateness of the lateral field borders was evaluated, inappropriateness was very frequently observed, both for AB (39.2%) and for PB (37.3%). In a study evaluating 25 sagittal MRI sections of patients with uterine cervix neoplasm, the presence of lesion beyond the PB was observed in six patients, demonstrating the relevance of the image in the evaluation of the lateral field borders[12].

Zunino et al. have applied the same method in the MRI analysis, utilizing a safety margin of 1.0 cm from the tumor and from the uterine fundus, and have found inappropriateness of PB in 49% and of AB in 8.8% of cases[7].

In another Brazilian study, inappropriateness indices corresponding to 46% (AB) and 40% (PB) have been observed[14]. Such results are similar to the ones observed in the present study. The same authors present an updating of these data with 80 patients, reporting 36% geographic miss in the AB, and 35% in the PB. In total, 56% of patients presented some kind of inappropriateness. In the present study, a significant relation was observed between field border inappropriateness and anteroposterior tumor diameter, displacement of the anterior rectal wall, and tumor volume. The authors suggest that such factors can be utilized as risk predictors of geographic miss[13].

As regards staging according to the FIGO classification, no significant influence from this factor on RT field borders appropriateness or inappropriateness was observed, maybe because of the absence of imaging studies such as computed tomography (CT) and MRI in this staging system[15]. However, the FIGO staging allows a standardization of the pretreatment assessment of patients in different regions of the world, even in locations where the access to more complex imaging methods is difficult, for comparison of therapeutic outcomes.

Another study has utilized the TNM staging system to evaluate the appropriateness of radiotherapy field borders, allowing the assessment of lymph nodes involvement. However, statistical analysis was not performed because of the low number of patients. Only a descriptive analysis was performed, demonstrating a high number of patients with staging T2B and absence of lymph nodes involvement[16].

As regards the analysis of each specific staging, the authors observed a high rate of inappropriateness in stages IIB (AB, 37.9% and PB, 34.4%) and IIIB (AB, 53.3% and PB, 46.6%), with no statistical significance. In the literature, Zunino et al. have observed staging inappropriateness in stages IB (AB, 0% and PB, 50%), IIA (AB, 0% and PB, 67%), IIB (AB, 5% and PB, 42%), IIIB (AB, 67% and PB, 33%) and IVA (AB, 0% and PB, 100%)[7].

Thus, the results of the present study demonstrate that the more advanced the staging, the more extensive the geographic miss. Maybe, a larger sample may provide a statistical evidence of these data.

As regards the histological grade that represents the tumor differentiation and plays a relevant role in the pretreatment evaluation of the disease, this parameter demonstrated a rate of inappropriateness of 33.3% (AB) and 0% (PB) in grade 1; 36% (AB) and 40% (PB) in grade 2; and 46.1% (AB) and 46.1% (PB) in grade 3. These results also demonstrate a greater planning error in higher histological grades, although this error is not significant. This finding may be correlated with the fact that higher histological grades are associated with more advanced or more voluminous

tumors. In the reviewed literature on radiotherapy field borders appropriateness evaluation with MRI, the authors have not evaluated this factor in relation to geographic miss[7,12,13].

Imaging methods such as CT and MRI would be indicated in the pretreatment evaluation for defining the tumor diameter and volume, and assessment of pelvic lymph nodes and parametrial invasion[17–20]. A meta-analyses of 57 studies demonstrated the higher sensitivity of MRI as compared with CT in the evaluation of parametrial invasion[21]. However, in a multicentric, prospective study with 208 patients with uterine cervix neoplasm submitted to clinical evaluation according to FIGO, helical CT and MRI compared with surgical (pathological) findings, the authors have observed that CT and MRI presented similar results in the evaluation of parametrial invasion, and have concluded that clinical examination was superior to other studies. The authors have suggested the imaging methods influence on the clinical staging, and that such imaging studies could improve the pretreatment staging of patients[22].

A recent study demonstrates the relevance of MRI as a prognostic factor in the analysis of the tumor volume and uterine invasion by the tumor, and of CT in the evaluation of positive pelvic lymph nodes[23].

The most recent National Comprehensive Cancer Network (NCCN) guidelines suggests the utilization of MRI and CT for defining the therapy planning, but these imaging methods do not influence the formal staging, and the FIGO staging is considered as a standard for comparison between treatments[24].

Thus, although the high cost of MRI for radiotherapy planning as a routine is one of the main factors which makes the implementation of this method more difficult in poor and developing countries, the results of the present study, in conjunction with the literature review, suggest that MRI plays an extremely relevant role in the radiotherapy planning for patients with uterine cervix neoplasm, and this planning should be individualized, considering the tumor volume and anatomical variations[7,12,13,16]. Uterine cervix cancer plays a relevant role as the third major cause of death in women worldwide, with about 274,000 yearly deaths, 78% of such deaths occurring in developing countries[1]. MRI can be beneficial to optimize the treatment of these patients.

CONCLUSIONS

As a whole, the results of the present study demonstrate that MRI is a relevant tool for radiotherapy planning in patients with uterine cervix cancer, allowing higher accuracy in the definition of irradiation field borders, thus reducing the incidence of geographic miss. According to the present results, the patient's age, tumor staging, histological type and grade are not related to the radiotherapy field borders inappropriateness.

REFERENCES

1. Parkin DM, Bray F, Ferlay J, et al. Global cancer statistics, 2002. CA Cancer J Clin. 2005;55:74–108.
2. Brasil. Ministério da Saúde. Instituto Nacional de Câncer. Estimativa 2010: incidência de câncer no Brasil. Rio de Janeiro, RJ: Instituto Nacional de Câncer; 2009.
3. Perez CA, Kavanagh BD. Uterine cervix. In: Perez CA, Brady LW, Halperin EC, et al., editors. Principles and practice of radiation oncology. 4th ed. Philadelphia, PA: Lippincott-Raven; 2004.
4. Oliveira JP, Rosa LAR, Batista DVS, et al. Avaliação da dose no reto em pacientes submetidas a braquiterapia de alta taxa de dose para o tratamento do câncer do colo uterino. Radiol Bras. 2009;42: 83–8.
5. Guimarães RGR, Carvalho HA, Stuart SR, et al. Avaliação dosimétrica de uma combinação de aplicadores para braquiterapia de tumores do colo uterino com acometimento da porção distal da vagina. Radiol Bras. 2009;42:209–14.
6. Swift PS, Hsu CJ. Cancer of the uterine cervix. In: Leibel SA, Philips TL, editors. Textbook of radiation oncology. 2nd ed. Philadelphia, PA: Saunders; 2004.
7. Zunino S, Rosato O, Lucino S, et al. Anatomic study of the pelvis in carcinoma of the uterine cervix as related to the box technique. Int J Radiat Oncol Biol Phys. 1999;44:53–9.
8. Mayr NA, Tali ET, Yuh WT, et al. Cervical cancer: application of MR imaging in radiation therapy. Radiology. 1993;189:601–8.
9. Thomas G, Ali S, Hoebers FJ, et al. Phase III trial to evaluate the efficacy of maintaining hemoglobin levels above 12.0 g/dL with erythropoietin vs above 10.0 g/dL without erythropoietin in anemic patients receiving concurrent radiation and cisplatin for cervical cancer. Gynecol Oncol. 2008;108:317–25.
10. Torres MA, Jhingran A, Thames HD Jr, et al. Comparison of treatment tolerance and outcomes in patients with cervical cancer treated with concurrent chemoradiotherapy in a prospective randomized trial or with standard treatment. Int J Radiat Oncol Biol Phys. 2008;70:118–25.
11. Huguet F, Cojocariu OM, Levy P, et al. Preoperative concurrent radiation therapy and chemotherapy for bulky stage IB2, IIA, and IIB carcinoma of the uterine cervix with proximal parametrial invasion. Int J Radiat Oncol Biol Phys. 2008;72:1508–15.
12. Russell AH, Walter JP, Anderson MW, et al. Sagittal magnetic resonance imaging in the design of lateral radiation treatment portals for patients with locally advanced squamous cancer of the cervix. Int J Radiat Oncol Biol Phys. 1992;23:449–55.
13. Justino PB, Baroni R, Blasbalg R, et al. Clinical tumor dimensions may be useful to prevent geographic miss in conventional radiotherapy of uterine cervix cancer – a magnetic resonance imaging-based study. Int J Radiat Oncol Biol Phys. 2009;74:503–10.
14. Justino PB, Carvalho HA, Baroni R, et al. Valor da ressonância magnética no planejamento radioterápico dos tumores de colo de útero: resultados preliminares. Radiol Bras. 2005;38:399–402.
15. Creasman WT. New gynecologic cancer staging. Gynecol Oncol. 1995;58:157–8.
16. Thomas L, Chacon B, Kind M, et al. Magnetic resonance imaging in the treatment planning of radiation therapy in carcinoma of the cervix treated with the four-field pelvic technique. Int J Radiat Oncol Biol Phys. 1997;37:827–32.
17. Greco A, Mason P, Leung AW, et al. Staging of carcinoma of the uterine cervix: MRI-surgical correlation. Clin Radiol. 1989;40:401–5.
18. Hawnaur JM, Johnson RJ, Carrington BM, et al. Predictive value of clinical examination, transrectal ultrasound and magnetic resonance imaging prior to radiotherapy in carcinoma of the cervix. Br J Radiol. 1998;71:819–27.
19. Toita T, Kakinohana Y, Shinzato S, et al. Tumor diameter/volume and pelvic node status assessed by magnetic resonance imaging (MRI) for uterine cervical cancer treated with irradiation. Int J Radiat Oncol Biol Phys. 1999;43:777–82.
20. Wagenaar HC, Trimbos JB, Postema S, et al. Tumor diameter and volume assessed by magnetic resonance imaging in the prediction of outcome for invasive cervical cancer. Gynecol Oncol. 2001;82:474–82.
21. Bipat S, Glas AS, van der Velden J, et al. Computed tomography and magnetic resonance imaging in staging of uterine cervical carcinoma: a systematic review. Gynecol Oncol. 2003;91:59–66.
22. Hricak H, Gatsonis C, Chi DS, et al. Role of imaging in pretreatment evaluation of early invasive cervical cancer: results of the intergroup study American College of Radiology Imaging Network 6651-Gynecologic Oncology Group 183. J Clin Oncol. 2005;23:9329–37.
23. Kim H, Kim W, Lee M, et al. Tumor volume and uterine body invasion assessed by MRI for prediction of outcome in cervical carcinoma treated with concurrent chemotherapy and radiotherapy. Jpn J Clin Oncol. 2007;37:858–66.
24. The NCCN Cervical Cancer Guideline, Version 1.2009. In: The Complete Library of NCCN Clinical Practice Guidelines in Oncology, 2009 [database on the Internet].