Is magnetic resonance imaging useful in early evaluation of women on neoadjuvant chemotherapy for locally advanced cervical cancer?

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Summary

Objective: To evaluate the accuracy of magnetic resonance imaging (MRI) in staging cervical tumors after neoadjuvant chemotherapy (NACT). *Methods:* 26 women, affected by locally advanced cervical cancer and triaged for surgery after NACT, were submitted to three cycles of neoadjuvant chemotherapy. All patients were submitted to MRI before and after NACT. We evaluated the MRI sensitivity and specificity in staging cervical tumors after chemotherapy, relating MRI findings after NACT with the pathological findings as the gold standard. *Results:* In our series, MRI sensitivity was 58.8% and specificity was 66.7%. *Conclusions:* In our study MRI accuracy after NACT was lower than that of MRI used to stage patients with early cervical cancer scheduled for primary surgery, reported by the literature. MRI false negative cases are the major problem because of the delay in application of an effective therapy in non responders to NACT.

Key words: Locally advanced cervical cancer (LACC); Neoadjuvant chemotherapy (NACT); Magnetic resonance imaging (MRI); Early response evaluation.

Introduction

Although the widespread availability of effective screening programs, cervical cancer ranks third worldwide among gynecological malignancies [1]. The optimal treatment strategies are increasingly tailored to the extent of disease, necessitating improvement in pretreatment evaluation [2].

For early cervical cancer (tumor limited to uterine cervix, International Federation of Gynecology and Obstetrics, FIGO, Stage Ia2-Ib1), radical surgery (radical hysterectomy and pelvic lymphadenectomy) or radiotherapy are accepted as the standard treatment. Instead, there is still no agreement on the best approach for bulky (maximum tumor diameter ≥ 4 cm) or locally advanced cervical cancer (LACC, FIGO Stage IIb-IVa) [3].

At present, concomitant chemoradiotherapy (CT-RT) is considered the standard treatment of LACC. A recent meta-analysis showed a highly absolute survival improvement of concomitant CT-RT compared to radiotherapy alone [4].

Recently, neoadjuvant chemotherapy (NACT) prior to surgery has been applied as a new therapeutic option for LACC. This treatment usually uses cisplatin-based agents repeated for three cycles at three-week intervals as the standard regimen. Some studies have supported its effectiveness in shrinking tumor size, controlling micrometastasis and increasing operability rate or improving the outcome of radiotherapy [5].

On the other side, major supposed disadvantages of NACT are the delay of curative treatment in non responders, the development of radio-resistant cellular clones, and the cross-resistance with radiotherapy [6].

How to make use of the advantages that NACT offers and at the same time how to avoid the delay of the effective therapy for non responders is a very important topic in current cervical cancer therapy. Early NACT response predictors are needed to provide a window of opportunity to modify treatment strategy and improve survival in non responders.

In recent years sophisticated radiological examinations, such as magnetic resonance imaging (MRI), have been used to define tumor extension before and/or after treatment so as to better tailor the management of patients affected by cervical cancer. However MRI in patients submitted to NACT seems to be less accurate than MRI used to stage patients with early cervical cancer triaged for primary surgery [7, 8].

The aim of this study was to evaluate the accuracy of MRI in staging cervical tumors after neoadjuvant chemotherapy and to analyze its usefulness in tailoring clinical management of women submitted to NACT.

Material and Methods

Between November 2002 and October 2010, 26 women affected by bulky or locally advanced cervical cancer and triaged for surgery after neoadjuvant treatment were admitted to the Unit of Clinical Obstetrics and Gynecology at the "San Martino" University Hospital in Genoa. These 26 patients were staged according to FIGO criteria and underwent a physical

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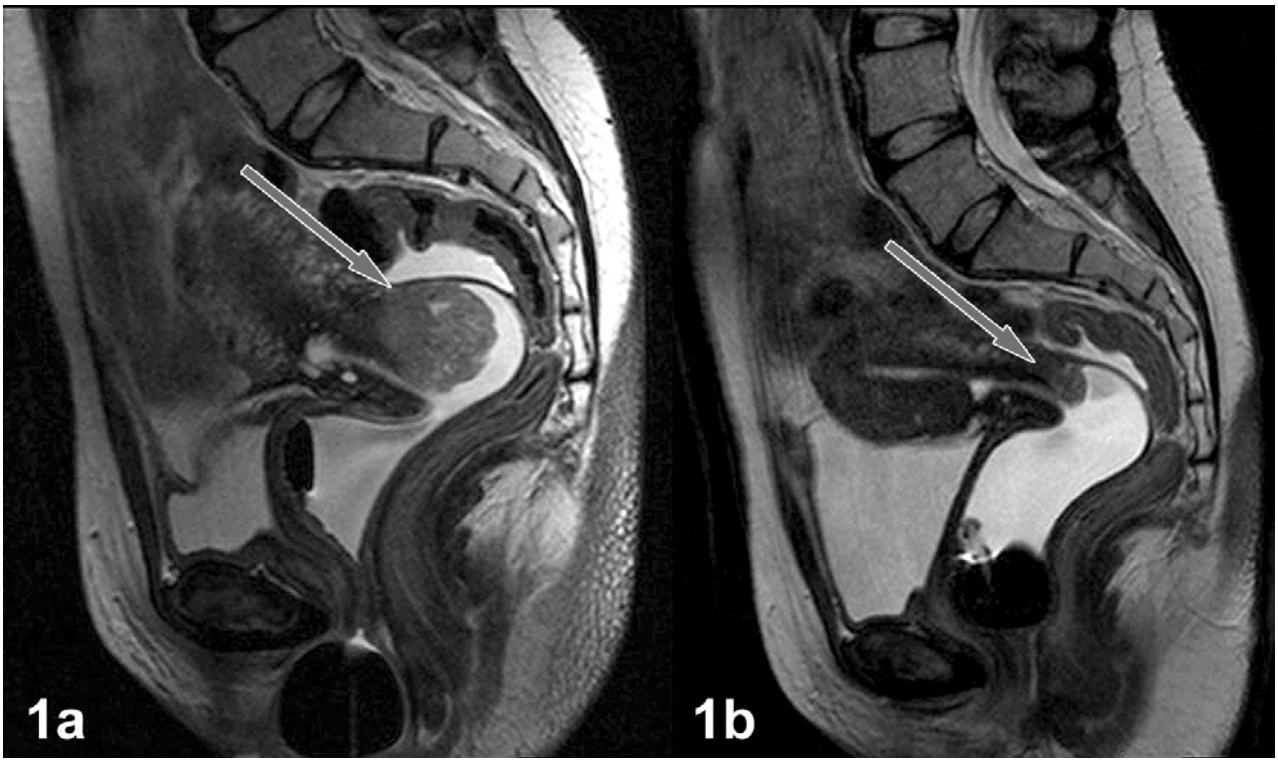

Figure 1. — A 29-year-old patient affected by locally advanced squamous cervical cancer, FIGO IIB (case n. 19 in Table 2 and n. 17 in Table 3). Sagittal T2-weighted MRI images with the auxilium of an artificial saline hydrocolpos, respectively, before and after neoadjuvant chemotherapy. In Figure 1a an esophytic tumor (arrow) can be seen located mainly on the cervical posterior labium with a 56 mm maximal diameter and infiltration of the left parametrium. Figure 1b documents only a small area of signal heterogeneity (arrow) on the cervical posterior labium after NACT. In this case there was correspondence between MRI, post-NACT, and pathological findings.

examination, tumor biopsy and chest X-ray. Clinical characteristics of the women enrolled in this study are reported in Table 1.

In all the cases the tumor staging was completed with an abdominal-pelvic MRI. In the last nine patients of the study the MRI exam was carried out, as now routinely performed in our Institution, with the auxilium of an artificial saline hydrocolpos [9]. MRI examinations were always performed and evaluated by the same radiologist. We used a high field MR scanner (Avanto 1.5 T, Siemens, Erlangen, Germany) with phased-array body coils. High resolution Turbo Spin Echo (TSE) T2-weighted sequences were performed (4 mm slice thickness, 200-220 field of view, matrix 256 x 256, TR 4000 ms, TE 90 ms, ETL 15, number of measurements 3, parallel imaging factor of acceleration 2) in sagittal, para-axial and para-coronal planes orientated towards the uterine cervix long axis. TSE T1-weighted axial images from the pelvis to the upper abdomen were then performed to evaluate the lymph nodes. Contrast medium was not used in any case.

Concerning imaging analysis, a tumor was identified when a signal that was equal to or higher than that of fat replaced low signal intensity of normal cervical stroma in the T2-weighted spin-echo images. Four MRI characteristics of cervical carcinoma were specifically recorded in the pelvic MRI by the radiologist:

– signal intensity in the T2-weighted images (equal to or higher than the surrounding adipose tissue);
– maximal diameter of the lesion;
– infiltration of vaginal fornices;
– infiltration of parametria.

Table 1. — *Clinical and pathological characteristics of the patients study (n = 26).*

Characteristics	Number (%) or mean (range)
Age (years)	45 (26-68)
Figo stage	
IB1	1 (3.8%)
IB2	5 (19.2%)
IIA	3 (11.5%)
IIB	16 (61.5%)
IIIA	0 (0%)
IIIB	1 (3.8%)
Histotype	
SCC[1]	22 (84.6%)
Adc[2]	4 (15.4%)
Grading of differentiation	
G1	2 (7.4%)
G2	13 (51.9%)
G3	7 (25.9%)
Unknown	4 (14.8%)

[1]SCC: squamous cell carcinoma; [2]Adc: adenocarcinoma.

The presence/absence of metastatic lymph nodes (considered positive if the nodal maximal diameter was more than 1 cm) was always reported.

All the 26 study women were submitted to three cycles of neoadjuvant chemotherapy. According to the age and performance status of the patients, they were treated with the TP schedule (paclitaxel 175 mg/m^2, cisplatin 75 mg/m^2) or the TIP sched-

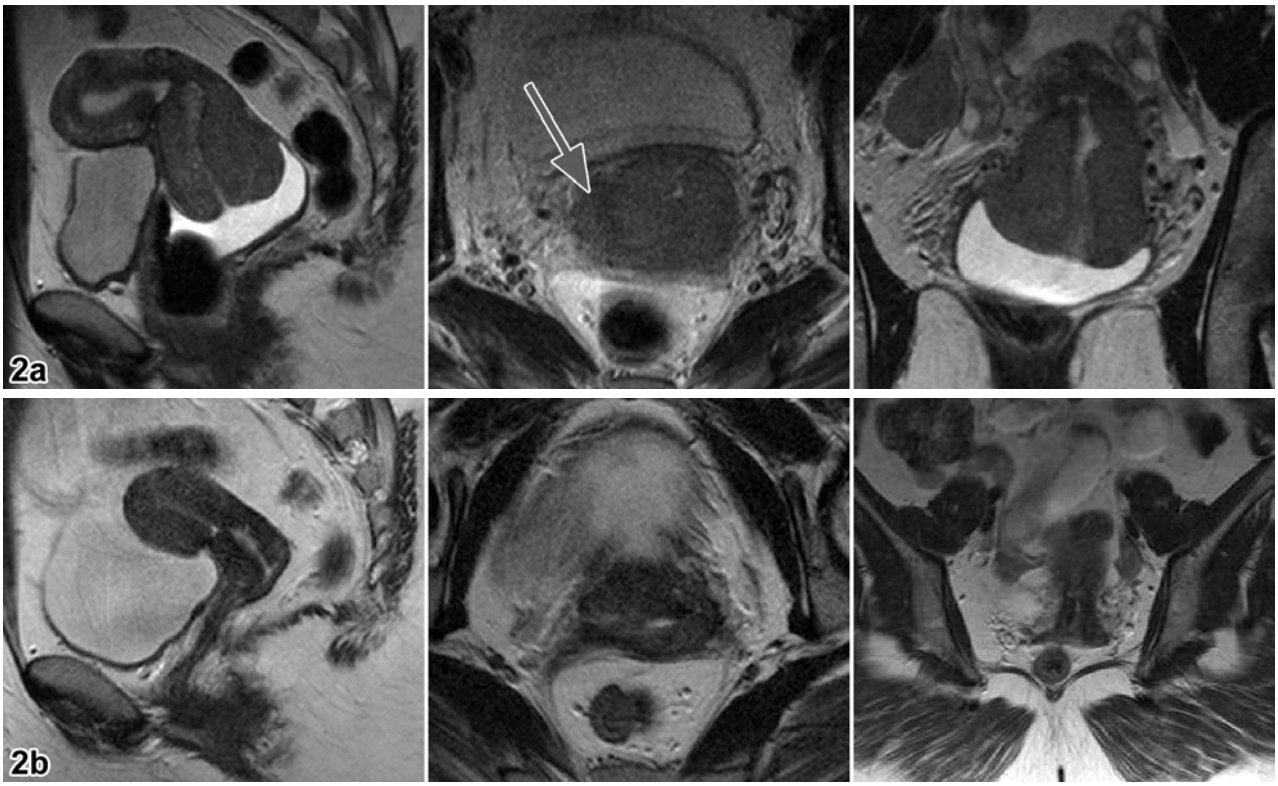

Figure 2. — A 36-year-old patient affected by locally advanced squamous cervical cancer, FIGO IB2-IIB (case n. 25 in Table 2 and n. 22 in Table 3). Figure 2a documents T2-weighted MRI sequences performed in the sagittal, para-axial and para-coronal planes with the auxilium of an artificial saline hydrocolpos before neoadjuvant chemotherapy. In these images a bulky tumor can be seen located mainly on the cervical posterior labium with a 61 mm maximal diameter; the presence of infiltration of the right parametrium is suspicious (arrow). Figure 2b shows the same MRI sequences but after NACT and without hydrocolpos: the minimal residual disease suggested by MRI was confirmed by the pathological findings (lesion maximal diameter of 7.5 mm).

ule (TP + ifosfamide 5 g/m^2). Twenty-three women were submitted to the TP regimen and the other three were submitted to the TIP regimen.

After the end of the neoadjuvant treatment every patient was reassessed using the same clinical and imaging procedures described above. All MRI studies after chemotherapy were performed within four weeks (mean 15 days) after the last course of chemotherapy. The MRI response to chemotherapy was recorded relating MRI findings before and after NACT, according to the World Health Organization (WHO) criteria [10]. A complete response (CR) was defined as the disappearance of all known disease, a partial response (PR) as a 50% or more decrease in total tumor size of the lesions and stable disease (SD) was identified when a 50% decrease in total tumor size could not be established nor a 25% increase in the size of one or more measurable lesions was not demonstrated. In conclusion progressive disease (PD) was defined as a 25% or more increase in size of tumor, or appearance of new lesions.

The patients who showed complete or partial MRI response to neoadjuvant treatment underwent surgery, while patients experiencing no change or progression of the disease were treated with salvage chemoradiotherapy.

Twenty-three out of the 26 patients were operated: 21 were submitted to Piver III radical hysterectomy, while the other two young patients (mean age 29.5 years old), wishing to retain their childbearing prospects, were treated with vaginal radical trachelectomy. In all these cases a pelvic and paraaortic lymphadenectomy was associated.

Adjuvant postoperative treatment was recommended to patients with pathological stage greater than pT2a, less than 3 mm of uninvolved cervical stroma or lymph node metastasis.

Three women were not operated because of SD and parametrial invasion at MRI after NACT. Thus these three patients were submitted to a definitive chemoradiation.

In the 23 patients who were operated, we evaluated the MRI sensitivity, specificity, false-negative rate and false-positive rate in staging cervical cancer after chemotherapy, relating MRI findings after NACT with the pathological findings as the gold standard. The correlation between MRI and pathological findings is about the extension of the tumor. For the pathological specimen, a tumor maximal diameter ≤ 3 mm is considered as microscopic disease and it is valued as a negative finding because its prognosis is equal to that of absent residual disease. A pathological residual disease with a maximal diameter > 3 mm is considered as macroscopic disease.

Results

In our study after NACT a MRI response (CR or PR) [10] was documented in 20 out of 26 patients (76.9%) (Table 2). Six patients demonstrated SD after chemother-

Table 2. — *Extension of the tumor at MRI pre- and post-NACT and MRI response to chemotherapy in the 26 study patients.* [1]*WHO response to chemotherapy: CR complete response, PR partial response, SD stable disease.*

Patient	MRI pre-NACT Maximal diameter (mm)	MRI pre-NACT Parametrial infiltration (yes/no)	MRI pre-NACT Lymphnode metastasis (yes/no)	MRI post-NACT Maximal diameter (mm)	MRI post-NACT Parametrial infiltration (yes/no)	MRI post-NACT Lymphnode metastasis (yes/no)	MRI response (CR, PR, SD)[1]
1	40	no	no	10	no	no	PR
2	38	yes	no	10	no	no	PR
3	60	yes	no	0	no	no	CR
4	60	yes	no	0	no	no	CR
5	60	yes	no	50	yes	no	SD
6	120	yes	yes	60	yes	yes	SD
7	49	yes	no	0	no	no	CR
8	60	yes	yes	0	no	no	CR
9	44	yes	no	20	no	no	PR
10	65	yes	yes	35	yes	yes	SD
11	59	yes	yes	0	no	no	CR
12	36	yes	no	15	no	no	PR
13	45	yes	no	20	no	no	PR
14	38	no	no	12	no	no	PR
15	58	yes	no	40	yes	no	SD
16	31	no	no	0	no	no	CR
17	50	yes	no	35	yes	no	SD
18	34	yes	yes	0	no	no	CR
19	56	yes	no	10	no	no	PR
20	46	yes	no	11	no	no	PR
21	57	no	yes	51	no	yes	SD
22	56	yes	yes	23	yes	yes	PR
23	29	yes	yes	0	no	no	CR
24	42	yes	no	10	no	no	PR
25	61	yes	yes	10	no	no	PR
26	53	yes	yes	14	no	no	PR

Table 3. — *Correlation between the MRI findings after NACT and the analysis of the pathological specimen in the 23 patients who were submitted to surgical intervention.* [1]*Correlation between MRI and pathological findings: TP true positive, FP false positive, TN true negative, FN false negative.*

Patient	MRI FIGO stage post-NACT	MRI lymphnode metastasis post-NACT	Pathological FIGO stage post-NACT	Pathological lymphnode metastasis post-NACT	MRI-pathology correlation (TP, FP, TN, FN)[1]
1	IB1	No	IB1	Yes	FN
2	IB1	No	IB1	No	TP
3	0	No	IIB	Yes	FN
4	0	No	0	No	TN
5	IIB	No	IIA	Yes	FN
6	0	No	IIB	Yes	FN
7	0	No	0	No	TN
8	IB1	No	IB1	No	TP
9	IIB	Yes	IIB	Yes	TP
10	0	No	IB1	No	FN
11	IB1	No	IB2	No	TP
12	IB1	No	0	No	FP
13	IB1	No	IB1	No	TP
14	IIB	No	IIB	No	TP
15	0	No	0	No	TN
16	0	No	0	No	TN
17	IB1	No	IB1	No	TP
18	IB1	No	IB1	No	TP
19	IIB	Yes	IB2	No	FP
20	0	No	IIB	No	FN
21	IB1	No	IB1	No	TP
22	IB1	No	IB1	No	TP
23	IB1	No	IB1	Yes	FN

apy with parametrial infiltration and/or lymph node metastasis: three out of these six women were not operated and were treated with salvage chemoradiotherapy (patients n. 6, 17 and 21 in Table 2); the other three patients and the gynecologists were in agreement about the surgical intervention (Piver III radical hysterectomy with pelvic and paraaortic lymphadenectomy) followed by adjuvant chemoradiotherapy (patients n. 5, 10 and 15 in Table 2). At MRI after NACT, a residual tumor mass was found in 18 out of 26 patients (69.2%). The mean tumor maximal diameter was 51.8 mm (range 29-120 mm) before NACT and 15.6 mm (range 0-60 mm) after chemotherapy.

In all the patients with macroscopic residual disease at MRI findings, the signal of the lesion was higher than that of fat in the T2-weighted images. MRI signal characteristics of the lesion were the same ones observed at the MRI examination before NACT.

We evaluated the MRI after NACT accuracy, comparing MRI findings with the analysis of the pathological specimen in the 23 patients who were operated after chemotherapy.

In our series there were seven false-negative cases (patients n. 1, 3, 5, 6, 10, 20 and 23 in Table 3). In particular MRI did not identify the presence of lymph node metastasis in three cases and did not determine parametrial infiltration in one case. In another two patients, MRI did not demonstrate the presence of any residual disease, while the pathological analysis documented a macroscopic residual lesion with parametrial infiltration and lymph node involvement (patients n. 3 and 6 in Table 3). In patient n. 10 (Table 3), MRI after NACT was negative for any residual disease but the pathological specimen identified a macroscopic lesion confined to the uterine cervix.

In our study the MRI sensitivity (true-positive patients at MRI ÷ positive patients at pathology %) in patients submitted to NACT was 58.8%. The false-negative rate (1 – sensitivity %) was 41.2%.

In one case (patient n. 19 in Table 3), MRI after NACT suggested the presence of parametrial infiltration with lymph node involvement, while the pathological analysis of the surgical specimen documented a bulky lesion confined to the uterine cervix, without other localizations. In patient n. 12 (Table 3) pathology did not confirm the presence of the macroscopic residual cervical lesion identified by MRI. In the end, patient n. 5 (Table 3) did not demonstrate parametrial infiltration at pathological analysis which MRI suggested.

In our series, MRI specificity (true-negative patients at MRI ÷ negative patients at pathology %) in patients submitted to NACT was 66.7%. The false-positive rate (1 – specificity %) was 33.3%.

Discussion

Today MRI is often used to complete the clinical staging of women affected by invasive cervical cancer. In

primary cervical carcinoma the overall accuracy for staging for MRI is 86% (for determining lesion diameters 93%, vaginal and parametrial invasion 95%, and the presence of nodal involvement 85%). Moreover, MRI is important for demonstrating treatment complications and for detecting of disease recurrence [2].

MRI is also used to evaluate tumor response after neoadjuvant treatment. In fact NACT represents a promising alternative option to standard chemoradiation for LACC, reducing the tumor size and increasing tumor resectability [5].

The rationales for the use of NACT are several. Tumor size reduction permits simplification of surgical procedures and the possible transformation of inoperable tumors in radically resectable ones. Also NACT may increase radiosensitivity decreasing hypoxic cell fraction. Some regimens, especially platinum-based ones, also act directly as radiation potentiators [11, 12].

Finally, response to NACT is an important prognostic factor and this helps in the decision making of the successive therapeutic approach [13].

However the efficiency and the safety of neoadjuvant treatment are currently controversial. Many women submitted to NACT also need adjuvant chemo and/or radiotherapic therapy, thus prolonging their treatment and potentially exacerbating associated morbidity.

Above all, the major problem of this new approach seems to be the delay of effective therapy for non-responders, submitted to three or four cycles of NACT during a period longer than nine weeks. In these women the delay may result in missing the optimal time point for surgery [5, 6, 14].

Thus, clinical and radiological evaluations of patients submitted to NACT are very important to plan the appropriate following treatment (radical surgery vs definitive chemoradiotherapy) and not to miss the optimal time point for definitive therapy in non responders.

In a study of Manfredi *et al*. MRI was performed before and after neoadjuvant therapy in 18 patients with locally invasive cervical carcinoma. MRI was 78% accurate in evaluation of tumor response [7].

In another study carried out by Testa *et al*. MRI after NACT was less accurate than MRI used to stage patients with early cervical cancer scheduled for primary surgery. Women treated with neoadjuvant therapy are difficult to examine with any imaging method because fibrosis and necrosis change the normal structure of the pelvic organs and disrupt the borders between organs and structures. Moreover the authors underlined that transvaginal ultrasonography (TVS) and MRI have a similar level of diagnostic performance, in contrast with studies in the past that suggested a very limited role for TVS examination in the evaluation of cervical cancer [15].

In our series of 26 patients we evaluated the performance of MRI in definition of size and parametrial or vaginal extent of invasive cervical cancer after NACT, with pathological findings used as the gold standard.

In our study MRI evaluation after NACT corresponded to the pathological one in 14 out of 23 patients (60.9%), with a sensitivity of 58.8%; in particular the false-negative rate (41.2%) was superior to that of the literature [7, 15].

In our series, we identified seven false-negative cases; most of all in two patients (n. 3 and 6 in Table 3), MRI did not demonstrate the presence of any residual disease, while the pathological analysis documented a macroscopic residual lesion with parametrial infiltration and lymph node involvement. Thus in these two cases the NACT approach delayed the application of an effective treatment and could have negatively influenced the survival chances of the patients. A correct MRI evaluation of the extent of residual disease could avoid surgical intervention.

The last nine patients in the study were evaluated with MRI completed by the auxilium of an artificial saline hydrocolpos, as now routinely performed in our Institution.

In MRI T2-weighted sequences, the elevated contrast intensity difference between the isotonic saline solution, which distends the vagina, and the lesion makes the evaluation of tumoral diameters, morphology (intra or extracervical growth) and of tumor relations with the nearest structures of the pelvis (internal uterine os, vaginal fornix and wall) more immediate and accurate (Figures 1 and 2).

Moreover in case of a large lesion that takes up all the vaginal cavity, fornix involvement evaluation can be very difficult. Hydrocolpos can precisely define the tumor infiltration at this level because the isotonic saline solution that distends the vagina interposes between the vaginal fornix and tumoral mass [9].

In our experience, hydrocolpos is a simple, cheap and safe artifact that makes the radiologist's interpretation of MRI scans easier and more immediate.

Conclusions

In our study MRI accuracy after NACT was lower than that of MRI used to stage patients with early cervical cancer triaged for primary surgery as reported by the literature [2].

MRI false-negative cases are the major problem in tailoring clinical management of women affected by uterine cervical cancer and submitted to NACT, because the false-negative case delays the application of an effective therapy in patients who do not respond to neoadjuvant therapy and thus salvage options are poor.

It may be useful to associate TVS examination to MRI after NACT and to repeat the staging workup after the first two cycles of chemotherapy, not to miss the optimal time point for definitive therapy in non responders.

With ongoing technological advances, functional imaging techniques, such as dynamic contrast enhanced MRI (DCE-MRI), diffusion weighted MRI, magnetic resonance spectroscopy and F-18-fluorodeoxyglucose positron emission tomography, have significant potential to provide new biomarkers of early tumor response, with an ultimate impact on cancer management [16-18].

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