

Magnetic Resonance Imaging for the Pre-Surgical Assessment of Endometrial Cancer: Results in a Routine Clinical Setting, Outside Dedicated Trials; a Cross-sectional Study

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Abstract. Aim: To assess the efficacy of magnetic resonance imaging (MRI) in predicting the surgical stage of endometrial carcinoma as a diagnostic tool, in a routine clinical setting, and not just in dedicated pilot studies or trials. Materials and Methods: The stage prediction made on MRI, as stated in the Radiology report, was compared with the effective surgical stage registered in the Pathology report. The 2009 International Federation of Gynecology and Obstetrics (FIGO) staging was used. Results: MRI and surgical stage correlated significantly ($p < 0.0001$, $r = 0.43$). However, there was only full concordance between predicted and true stage in 47.2% (43/91) of cases. Conversely, 11% (10/91) of cases were overstaged by MRI, whereas 41.8% (38/91) were understaged. For type-I tumors, where the decision to perform lymphadenectomy or not is crucial, there was full concordance in 63.9% of cases. What is more important, neither understaging (eight cases), nor overstaging (five cases) by MRI would have resulted in modification of the global treatment schedule, and thus potentially of prognosis. However, five patients would have undergone unnecessary surgery. On the other hand, half of the patients would have been correctly spared extended surgery. Conclusion: If restricted to type-I tumors, pre-surgical MRI appears useful under routine clinical conditions, and helps avoid unnecessary surgery in 50% of selected cases.

Magnetic resonance imaging (MRI) has entered the routine clinical setting for the pre-surgical assessment of patients with endometrial carcinoma. This has been due to the

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relatively high correlation found between the stage predicted by MRI and the final surgical stage in a number of pilot studies, including some conducted by our group (1, 2). In particular, the depth of myometrial invasion as predicted by MRI is claimed to allow for a better tailoring of the surgical strategy to be employed, and most notably, indicate the need to carry-out a lymphadenectomy or not, to complement the standard hysterectomy and bilateral salpingoophorectomy. This is not a minor question, since the morbidity associated with a complete staging procedure, still advocated in intermediate- and high-risk cases (3), is by no means negligible. The vast majority of patients with endometrial carcinoma belong to the advanced-age group, are more often than not obese, and tend to have associated pathologies, such as diabetes. This makes them prone to intraoperative and postoperative complications and consequently to a prolonged hospital stay, that poses a huge burden on them individually, and on the healthcare system as a whole.

Significant developments have taken place that may change the whole philosophy surrounding the most adequate treatment of endometrial carcinoma. The first has been the recognition of two clinically different endometrial carcinoma types (accordingly called type-I and type-II), with distinct, indeed opposed, natural histories (4). Whereas type-I carcinomas tend to have a more indolent course and to be associated with a significantly better prognosis, their type-2 counterparts are extremely aggressive, and exhibit a behavior reminiscent of ovarian carcinoma. The surgical approach towards each type, consequently, follows entirely different directions. The second development has to do with the question of the still prevalent paradigm that mandates for a complete staging procedure, including pelvic and para-aortic lymphadenectomy in every case. This follows the publication of the results from two randomized trials studying the usefulness of lymphadenectomy in endometrial carcinoma (5, 6). The evidence provided by these two studies, which

constitutes the first ever published level-I evidence on this issue, strongly brings into question the currently accepted, and recently modified, International Federation of Gynecology and Obstetrics (FIGO) staging system for this kind of cancer. The use of MRI in this context is directly related to the fundamental question raised by these randomised trials, since it is primarily used for selecting patients presumed to benefit from an extended surgical procedure including lymphadenectomy.

With this in mind, we reviewed our own experience with the now-routine use of pre-surgical MRI in patients with endometrial carcinoma, in order to evaluate its efficacy in light of the above-mentioned developments regarding the clinical management of this tumor type. Another important issue we addressed was the true degree of precision of MRI for predicting the final stage pre-surgically once this procedure has entered clinical routine, and thus is not always performed by a dedicated small team involved in a pilot trial, but rather by different members of the corresponding Radiology Departments, including differently skilled individuals, who must deal with a variety of diagnostic tools and different pathologies as part of their daily work.

Patients and Methods

The clinical charts of all our patients with endometrial carcinoma operated upon between 1st January 2007 and 31st December 2011 who had undergone a nuclear magnetic resonance study prior to their surgery were reviewed. A 5-year follow-up period after closure of data sampling was allowed before closure of the study on 31st December 2015 in order to evaluate patient survival. Uterine sarcoma cases were excluded from the study. We then compared the stage prediction made on MRI, as stated in the Radiology report, with the effective surgical stage registered in the Pathology report. In all, 91 MRI studies were performed on an equal number of patients subsequently operated upon. The histologies were as follows: endometrioid, 70; papillary serous, five; clear cell, three; mixed, 13. The latest FIGO staging of 2009 was used, which regroups the former IA and IB stages into a single stage (7). The correlation between the stage predicted by MRI, and the true surgical stage was studied by means of Spearman's rank correlation test. In order to perform the statistical correlation study, the stage classification, both that predicted by the MRI, and the true one emanating from the final Pathology report, was simplified and converted into a numerical continuum as follows: stage IA=1; IB=2; II=3 and disease outside the uterus, regardless of stage=4. Differences in the distribution of higher-stage cases between groups were calculated by means of Fisher's exact test. Differences in the survival of patients were calculated by means of the Kaplan–Meier method and the log-rank test. The obtained values were considered significant when the p -value was less than 0.05.

Results

The results of the present study disclosed a significant correlation between tumor stage, as predicted by MRI, and surgical stage ($p < 0.0001$, $r = 0.43$), which, however, was only

marginally better than that found between tumor grade and surgical stage ($p = 0.0001$, $r = 0.40$). In fact, there was only full concordance between the predicted and true stage in 47.2% (43/91) of cases. Conversely, 41.8% (38/91) were understaged (Table I), whereas 11% (10/91) of cases were overstaged by MRI (Table II). The subgroup of type-I endometrial carcinomas was analyzed separately, and the results of this subanalysis are given in Table III. In this subgroup, full concordance between MRI-predicted and true stage was considerably better (63.9%). Importantly for this particular cohort of patients, neither understaging (eight cases), nor overstaging (five cases) by MRI would have resulted in modification of the global treatment schedule, and thus potentially of prognosis.

Agreement or not of MRI and final stage was not associated with survival. A crude first analysis disclosed an almost significant ($p = 0.07$) difference between full agreement of the stage predicted by MRI and the final surgical stage, but this was only so because the discordant group contained significantly ($p = 0.0005$) more advanced-stage cases, with disease outside the uterine cavity, which makes diagnosis by means of imaging methods inherently more difficult. In fact, when the survival analysis was restricted to surgical stage-I cases, *i.e.*, disease confined to the uterine cavity, the difference completely disappeared ($p = 0.6$).

Discussion

The relatively poor agreement between the stage predicted by MRI and the final surgical stage in our series of patients with endometrial carcinoma may be surprising at first sight when compared to previous reports, some of them by our own group (1, 2). This rate of discrepancy may seem unacceptable, if MRI is to be used for tailoring the surgical approach in endometrial carcinoma. However, if one analyzes the results considering their real influence on the clinical management of these patients, the picture is quite different. In fact, as can be seen from Table I, if we had relied exclusively on the pre-surgical MRI study, and had restricted full surgical staging, including lymphadenectomy, to cases in presumed stage IB or higher, as mandated by current protocols, only two cases with involved nodes requiring a more aggressive modification of the postoperative treatment schedule would have gone unrecognized. These cases, which might have been missed because of insufficient surgery, are the really significant ones from the clinical point of view, since their prognosis could have theoretically been worsened by not receiving additional treatment. This makes up for a clinically relevant mis-staging rate of 2.2%, which may seem unacceptable to many, but is not as alarming as the crude discrepancy rate of 52.8% cited above. Overstaging, resulting in unnecessary surgery in 5/10 cases (Table II), does not result in a clinical harm to patients, apart

Table I. Endometrial carcinomas understaged by magnetic resonance imaging (MRI). 2009 International Federation of Gynecology and Obstetrics surgical staging system (7).

Case no.	Stage predicted by MRI	Final stage
1	IA	IB
2	IA	IB
3	IA	IB
4	IA	IB
5	IA	IB
6	IA	IB
7	IA	IB
8	IA	IB
9	IA	IB
10	IA	IB
11	IA	IB
12	IA	IB
13	IA	IB
14	IA	II
15	IA	II
16	IA	II
17	IA	II
18	IA	IIIA
19	IA	IIIA
20	IA	IIIA
21	IA	IIIA
22	IA	IIIC#
23	IA	IIIC#
24	IB	II
25	IB	II
26	IB	II
27	IB	II
28	IB	IIIA
29	IB	IIIA
30	IB	IIIA
31	IB	IIIA
32	IB	IIIB
33	IB	IIIC*
34	IB	IIIC*
35	II	IIIA
36	II	IIIC*
37	IIIB	IIIC*
38	IVA	IVB

*Correct surgical strategy indicated by MRI modifies adjuvant therapy;
#higher stage requiring additional treatment unrecognized by magnetic resonance imaging.

from the higher risk inherently associated with extended surgery, since it does not influence their receiving additional treatment or not.

The sub-analysis carried out for type-I carcinomas, moreover, is highly interesting from the practical point of view. In fact, the strategy used in many, if not most, centers is to submit all patients with type-II endometrial carcinoma to complete surgical staging, if this is technically feasible, because they are those most likely to have disease outside the uterus and to benefit potentially from additional

Table II. Endometrial carcinomas overstaged by magnetic resonance imaging (MRI).

Case no.	Stage predicted by MRI	Final stage
1	IB	IA*
2	IB	IA*
3	IB	IA*
4	IB	IA*
5	II	IA*
6	II	IB
7	II	IB
8	IIIA	IB
9	IIIC	IB
10	IVA	IIIA

*Would have undergone unnecessary surgery.

Table III. Type-I endometrial carcinomas staged by magnetic resonance imaging (MRI).

Case no.	Stage predicted by MRI	Final stage
1	IA	IA
2	IA	IA
3	IA	IA
4	IA	IA
5	IA	IA
6	IA	IA
7	IA	IA
8	IA	IA
9	IA	IA
10	IA	IA
11	IA	IA
12	IA	IA
13	IA	IA
14	IA	IA
15	IA	IA
16	IA	IA
17	IA	IA
18	IB	IB
19	IB	IB
20	IB	IB
21	IB	IB
22	IB	IB
23	II	II
24	IA*	IB
25	IA*	IB
26	IA*	IB
27	IA*	II
28	IA*	II
29	IA*	II
30	IA*	IIIA
31	IB*	IIIA
32	IB#	IA
33	IB#	IA
34	II#	IB
35	II#	IA
36	IIIC#	IB

*Understaged by MRI; #overstaged by MRI.

treatment. This includes all papillary serous and clear-cell carcinomas, together with all undifferentiated, grade 3 endometrioid carcinomas. Therefore, the question of whether to perform extended surgery or not would remain limited to grade 1 and grade 2 (type-I) endometrioid carcinomas, and it is in these cases where the predictive value of MRI is relevant, because lymphadenectomy in these patients could potentially be restricted to those with presumed deep myometrial invasion by the tumor. As can be seen from Table III, the results in this setting, that is particularly relevant from the clinical point of view, are far better than for the whole group. Indeed, there was full concordance between MRI-predicted and final stage in 63.9% of cases. However, five patients would still have undergone unnecessary surgery. On the other hand, half of the patients would have been correctly spared extended surgery, which represents a considerable potential benefit, if we had fully relied on MRI for decision-taking.

All in all, our results appear to represent a modest potential improvement in patient management. They also seem to contradict our own initial optimism (1, 2), derived from pilot studies, once MRI has fully entered clinical routine. However, a report from a Swedish tertiary-care, University-based center similar to the one in which this study was carried out provides a plausible explanation for such a discrepancy, once an enthusiastic and dedicated clinical research activity is transferred to daily hospital practice. In fact, Haldorsen *et al.* submitted MRIs from patients with endometrial carcinoma for diagnosis in a blinded fashion to three radiologists from the same Department of their center, and the agreement ratios, both between each other and with the corresponding pathology report were modest at best, and largely comparable to those reported in the present study (8). Finally, a recent study by Tanaka *et al.* (9) presents results that are largely coincident with our own ones, in that MRI may be still useful, but inferior to intraoperative histological analysis in guiding surgical decisions, if restricted to early-stage, well-differentiated endometrial carcinomas of the endometrioid variety.

In conclusion, as our sub-analysis showed, in practical terms, that MRI may still be useful for the correct management of patients with endometrial carcinoma even in a routine clinical setting. MRI can prove particularly helpful by preventing unnecessary lymphadenectomies, if MRI-based pre-surgical evaluation is restricted to type-I tumors, assuming that type-II tumors have to undergo extended surgery anyhow. Even this strategy may be obsolete in the near future, if we fully accept the results of the only two randomized clinical trials published on the usefulness of

lymphadenectomy in early endometrial cancer (5, 6). In both of them, no improvement in survival was found to be associated with the performance of lymphadenectomy (and the corresponding modification of treatment following the diagnosis of invaded nodes). Consequently, a surgical measure that carries with it a prolonged surgical time, higher risks and higher costs should be seriously questioned, at least until trials with the same degree of evidence show otherwise.

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