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FULL PAPER

MRI may be used as a prognostic indicator in patients with extra-abdominal desmoid tumours

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Objective: To determine the association of MRI features of extra-abdominal desmoid tumours (DTs) with prognosis.

Methods: MRIs for 90 patients with DT were retrospectively reviewed for imaging features associated with biological behaviour. The primary end point was progression (for lesions managed with chemotherapy, radiation therapy and observation) or recurrence (following surgery). Time to event was studied using univariate and multivariable Cox proportional hazards regression models when accounting for demographic, clinicopathological and imaging variables. Kaplan-Meier plots were used to estimate event-free rate (EFR).

Results: Univariate analysis revealed a significant relationship between EFR and treatment, location and compartment of origin [subcutaneous (SC), superficial fascial, intramuscular (IM) and deep fascial/intermuscular]. None of the imaging features commonly associated with biological behaviour of DTs (e.g., shape, enhancement, T_2 signal etc.) or surgical margins (in surgical cases) was associated with EFR. Multivariate analysis

showed that treatment modality and compartment of origin were independent predictors of EFR. Superficial and deep fascial lesions had a significantly worse EFR as a group [hazard ratio: 3.9; 95% confidence interval (CI): 1.83–8.32; $p = 0.0004$] than did the SC and IM lesions as a group. 5-year EFR for the fascial lesions was 18% (95% CI: 6–36%), compared with 57% (95% CI: 25–79%) for the SC and IM groups.

Conclusion: Intramuscular or SC DTs may be associated with improved prognosis. If validated on multireader and prospective studies, these results can provide for rapid risk stratification at the time of initial MRI.

Advances in knowledge: This work has shown that imaging features commonly associated with biological activity of desmoid tumours (e.g. shape, T_2 signal and enhancement) do not appear to be associated with prognosis in patients undergoing a variety of treatment modalities. The compartment of origin of the lesion, which can be determined on pre-operative MRI, was shown to be associated with prognosis and can allow for risk stratification in patients with DTs.

INTRODUCTION

Extra-abdominal desmoid tumours (DTs) are benign monoclonal proliferations of fibroblasts with unpredictable clinical behaviour.^{1,2} They can be locally aggressive and lead to pain, deformity, organ dysfunction and, in rare cases, death.^{3,4} They can also follow a less aggressive

natural history characterized by stability and spontaneous regression.⁵ Currently, there is no readily available method for assessment of biological activity of extra-abdominal DTs. This has led to uncertainty on optimal management for these tumours, and various combinations of observation, systemic therapy, radiation therapy (RT) and surgery

are currently in use.^{6–8} More recently, a front-line wait-and-see approach has been advocated.⁸

Different variables have been proposed for determination of prognosis in patients with extra-abdominal DTs, including age,^{6,9,10} tumour size,^{9–13} tumour location,^{9,10,12–15} surgical margins,^{6,14–20} compartmentalization,²¹ and various genetic and immunohistological features.^{19,22–25} However, the results of some of these studies have been contradictory, and other studies have failed to demonstrate clinical variables as being useful prognostic factors.^{26–30}

Imaging provides a readily available method for assessment of biological activity, which may enable rapid risk stratification, selection of optimal therapy and determination of efficient follow-up interval after therapy. MRI offers a non-invasive modality that can be used to assess the global characteristics of lesions and is currently in wide use as the imaging modality of choice in assessment of soft-tissue lesions of the extremities and trunk. Its use as a prognostic marker in DTs has been limited, however.³¹ MRI features thought to be associated with biological behaviour of desmoid tumours include infiltrative shape, indistinct margins and the extent and intensity of T_2 hyper-intensity and enhancement.

The goal of this study is to retrospectively determine the association of MRI features of extra-abdominal DTs with event-free rate (EFR), with the assumption that EFR will offer a secondary, albeit imperfect, assessment of biological behaviour. The expectation is that this will serve as a first step in designing prospective studies to assess the use of MRI for determining biological behaviour of these lesions, and risk stratifying patients for selection of front-line observation *vs* therapy. The central hypothesis is that MRI features in treatment-naïve patients with extra-abdominal DTs can be used to risk stratify patients based on EFR.

METHODS AND MATERIALS

A waiver of informed consent and waiver of authorization to use and disclose protected health information was requested from the MD Anderson Cancer Center institutional review board and granted for this retrospective study.

Study population

The study population was drawn from the tumour registry of MD Anderson Cancer Center by searching for the diagnosis of DT from the period spanning 1 January 2000 through 1 April 2013. From an initial set of 542 patients, 90 patients met the inclusion criteria and were used in the final analysis. Inclusion criteria included: extra-abdominal location of tumour (*i.e.* abdominal wall, trunk and limb, but not intra-abdominal or intrathoracic), availability of pre-therapy MRI (*i.e.* no history of systemic or local therapy including excisional biopsy prior to MRI) and at least 6 months of follow-up.

Data collection

Clinical and pathological data were obtained from the electronic medical record and a pathology database. The categorical variables for the demographic and clinical variables collected are

Table 1. Summary demographic and clinical statistics for study population

Variable	Number
Gender	
Female	57 (63%)
Male	33 (37%)
Race	
Asian	5 (6%)
Black	3 (3%)
Hispanic	9 (10%)
White	73 (81%)
Treatment	
Observation	2 (2%)
Surgery alone	49 (54%)
XRT alone	8 (9%)
XRT + surgery	5 (6%)
Chemo: conventional	7 (8%)
Chemo: hormonal	1 (1%)
Chemo: TKI	2 (2%)
Chemo: Hormonal + TKI	2 (2%)
Conventional chemo + surgery	2 (2%)
Conventional chemo + XRT	1 (1%)
Other (with surgery)	4 (4%)
Other (no surgery)	7 (8%)
Location of surgery ($n = 60$)	
Unknown	2 (3%)
MDACC	35 (58%)
Outside facility	23 (38%)
FAP	
Yes	1 (1%)
No	89 (99%)
Type of surgeon ($n = 60$)	
Unknown	4 (7%)
Oncological	47 (78%)
Non-oncological	9 (15%)
Surgical margins ($n = 60$)	
Negative	13 (22%)
Close (5–10 mm)	12 (20%)
Positive (<5 mm)	35 (58%)
CTNNB1 mutation status	
N/A	43 (48%)
WT	8 (9%)

(Continued)

Table 1. (Continued)

Variable	Number
p.S45F	16 (18%)
p.S45P	3 (3%)
p.T41A	20 (22%)
Treatment start date	
2001	1 (1%)
2002	4 (4%)
2003	2 (2%)
2004	3 (3%)
2005	8 (9%)
2006	4 (4%)
2007	10 (11%)
2008	8 (9%)
2009	13 (14%)
2010	10 (11%)
2011	10 (11%)
2012	13 (14%)
2013	4 (4%)

Chemo, chemotherapy; FAP, familial adenomatous polyposis; MDACC, MD Anderson Cancer Center; N/A, not available; TKI, tyrosine kinase inhibitor; WT, wild-type; XRT, radiation therapy. Percentages may not sum up to 100 because of rounding.

shown in Table 1. Demographic data collected included race, gender and birth date. Pathological data collected included final diagnosis and β -catenin mutation status (wild-type, p.S45F, p.S45P, p.T41A). Clinical data collected included treatment history, initial treatment (start and end dates), location of surgery (unknown, MD Anderson Cancer Center, outside facility), type of surgeon (unknown, oncological, non-oncological) and surgical margins [negative (>1 cm), close (5 mm–1 cm) and histologically positive]. For lesions resected at an outside facility, type of surgeon was determined from the practice or hospital name on scanned operative reports and/or internet search of the surgeon's name for description of practice. In order to eliminate variability in recurrence or progression date because of variability in image interpretation quality, the actual recurrence date was determined by a single musculoskeletal radiologist (BA) who assessed all imaging data prior to and including the reported date of clinical recurrence or progression. This included review of pre-therapy MRI; however, assessment for progression or recurrence was performed after review of the pre-therapy MRI for determination of imaging characteristics at baseline.

Image analysis

The following semi-quantitative data were obtained from the pre-therapy MRI by two readers (FK and BA: 2 and 7 years' of experience interpreting images, respectively) in consensus: location, depth, compartment of origin [Figure 1, defined as

subcutaneous (SC), superficial fascial, intramuscular (IM) and deep fascial/intermuscular], confinement to the compartment of origin (Figure 1), multifocality (a lesion was considered multifocal if at least 1 cm of definitively normal tissue on all available pulse sequences separated the different components), dominant shape (round/oval, lobulated and infiltrative), dominant margin (pseudocapsule, well defined, indistinct), proportion of the margin that was infiltrative or indistinct, dominant T_2 signal, proportion of T_2 signal that was equal to or greater than muscle or fluid, degree of enhancement and the proportion of the lesion that enhanced. Proportions were subjectively graded as less than one-third, between one-third to two-thirds and greater than two-thirds of the lesion volume. Two- and three-dimensional measurements of the lesions were attempted early in the course of the study, but were abandoned due to significant inter- and intrareader variability due to the infiltrative and ill-defined margins of the lesions. Instead, the longest dimension of lesions (using all available imaging planes) was measured by consensus. The entirety of the lesion, including areas of low signal on all pulse sequences, was included for measurement. For multifocal lesions, the largest lesion was measured. For scanned images from outside facilities, calipers were calibrated to rulers provided on the images prior to measurement. Imaging assessment was performed prior to determination of the final status of the patient (e.g. progression or recurrence).

Statistical analysis

The primary end point was recurrence for surgically treated lesions and progression for lesions treated with chemotherapy or radiation therapy or undergoing observation. Recurrence after surgery was defined as the appearance of an enhancing lesion in or near the resection bed that was either biopsy proven to represent disease or enlarged on subsequent studies. Progression was defined as enlargement of a lesion not otherwise accounted for by technical factors. Univariate and multivariable Cox proportional hazards regression models were used to assess the relationship between these variables and time to event. The start time was the date of surgery or the date when radiation or chemotherapy was initiated. For patients managed with observation, the start time was the date of first MRI. To assess the possibility that effect of confinement to compartment was apparent only among responders or non-responders, we performed a Cox proportional hazards model that included an interaction term between compartment of origin (two levels: IM/SC *vs* superficial/deep fascial) and confinement (yes *vs* no) along with the main effects for compartment and confinement. We also fit a model with only the interaction and not the main effects.

Kaplan–Meier plots were used to estimate EFR. A log rank (Mantel–Cox) test was used to determine if there were differences in the survival distribution for the different types of compartment of origin, first individually and then as two groups (IM/SC and superficial/deep fascial). Fisher's exact tests were used to analyse the association between imaging features and mutation status (p.S45F *vs* other). All statistical analyses were performed using SAS® v. 9.3 (SAS Institute Inc. Cary, NC) for Windows® (Microsoft, Remond, WA).

Figure 1. Definition of compartment of origin and containment within compartment of origin. The left panel is a diagram of the soft tissues extending superficial to deep from top to bottom (subcutaneous, superficial fascial, intramuscular and deep fascial/intermuscular). Types of lesions are also illustrated. The right panel provides MRI examples of the different types of lesions. 1, subcutaneous lesion confined to its compartment of origin; 2, subcutaneous lesion extending beyond its compartment of origin; 3, superficial fascial lesion confined to its compartment of origin; 4, superficial fascial lesion extending beyond its compartment of origin; 5, intramuscular lesion confined to its compartment of origin; 6, intramuscular lesion extending beyond its compartment of origin; 7, deep fascial lesion confined to its compartment of origin; 8, deep fascial lesion extending beyond its compartment of origin; arrowheads, areas of extracompartmental infiltration; white arrows, primary lesions; black arrow, second lesion.

RESULTS

The study population and interventions are shown in Figure 2 and summarized in Table 1. A total of 90 patients were followed for a mean duration of 42.3 months (range 6–108 months) following the initial imaging study. The majority of patients (71%) initiated treatment between 2007 and 2012. *CTNNB1*

mutation status was available in 47 patients (52%). A plurality of those tested had the p.T41A mutation, followed by the p.S45F and p.S45P mutations.

MR images were reviewed from first presentation to the last available image or reported date of recurrence to determine the

Figure 2. Study population and interventions. Other ($n = 7$) indicates included patients who were managed with combinations of systemic therapy, radiation therapy and surgery that did not fit with the categorization scheme. Chemo, chemotherapy; DT, desmoid tumour; FU, follow-up; MDACC, MD Anderson Cancer Center; non-onc, non-oncological; OSF, outside facility; XRT, radiation therapy.

Figure 3. Location of lesions. Underlined text indicates that lesions at these locations were considered to be located in the trunk (as opposed to extremity). One patient had an infiltrative lesion that extended from the chest wall to the shoulder, and is not included in this diagram.

* 1 patient (1%) had a lesion that involved both the chest wall and the shoulder

actual date of recurrence (for surgically treated lesions) or progression (for all others). There were 44 cases of recurrent or progressive disease (49% of the total). In 10 of these 44 cases (23%), recurrence or progression was visible on MRI prior to being first noted on the MRI reports. The reasons for this discrepancy and the lessons learned are the subject of a separate report.³²

MR images were assessed for location of the primary tumour and imaging features believed to be associated with biological behaviour. Slightly more than half (54%) of the lesions were located in the trunk (Figure 3), which included lesions in the neck (14%), axilla (11%), anterior abdominal wall (10%), chest wall (8%), back (8%), breast (2%) and scalp/face (1%). Extremity lesions were located in the thigh (12%), upper arm (10%), lower leg (7%), shoulder (6%), forearm (6%), buttocks (2%) and hand (2%). One patient had an infiltrative lesion that extended from the chest wall to the shoulder and could not be definitively classified as originating from either location.

The assessed MRI features associated with biological behaviour of DTs are shown in Figure 4. Univariate analysis of these imaging features, along with demographic and clinicopathological variables, was performed. For the location variable, one lesion was excluded, as it spanned the chest wall and shoulder, without an obvious origin. For the treatment variable, the two patients managed with observation were excluded, as their low numbers precluded analysis and their management did not fit into other therapeutic categories. For the compartment of origin variable, one lesion was excluded, as its compartment of origin could not be reliably demonstrated without the ability to window images on scanned films from an outside facility.

There was a significant relationship between EFR and treatment, location and compartment of origin on univariate analysis (selected results shown in Table 2). Multivariate analysis of these variables showed a significant relationship remained between EFR and compartment of origin after accounting for treatment modality. Specifically, the superficial or deep fascial lesions had a significantly worse EFR (hazard ratio: 3.9; 95% CI: 1.83–8.32; $p = 0.0004$) than those with IM or SC compartments of origin after accounting for location and treatment modality. The 5-year EFR for the fascial lesions was 18% (95% CI: 6–36%) compared with 57% (95% CI: 25–79%) for the lesions with an IM or SC compartment of origin.

We next assessed if a lesion's confinement to its compartment of origin could have an impact that was apparent only among responders or non-responders. Inclusion of an interaction between compartment of origin and confinement in a Cox regression model either with or without the main effects for compartment and confinement showed no evidence of a significant interaction ($p = 0.65$ and $p = 0.20$, respectively).

Kaplan–Meier analysis showed that the median time to event (recurrence or progression) for the fascial lesions was 1.5 years (95% CI: 0.99–2.49). The median time to event for the IM and SC groups could not be estimated, as its curve did not fall <50% during the observation period (Figure 5). There was a significant difference between the curves based on compartment of origin, with SC and IM lesions portending a better EFR than superficial or deep fascial lesions.

DISCUSSION

We studied the relationship between imaging features on pre-treatment MRI with EFR in patients with DTs, while taking into

Figure 4. Summary of imaging features. IM, intramuscular; N/A, not available; SubQ, subcutaneous.

account various demographic and clinicopathological features (Table 1) that could act as confounding factors. Our results showed that compartment of origin (Figure 1), as determined on pre-therapy MRI, is an independent prognostic factor for EFR (Table 2). Specifically, we found that tumours originating from the SC or IM compartments resulted in significantly better EFR durations than those originating from superficial or deep fascial planes (Figure 5). This relationship was not affected by whether or not the lesions were confined to their compartments of origin, suggesting an inherent difference in the biological activity of these two classes of DTs, and not necessarily the mechanical barrier effect of an intact fascia.

The association of the compartment of origin of a soft-tissue lesion with biological behaviour has previously been described by Enneking et al³³ for soft-tissue sarcomas, who noted that lesions arising in intercompartments (or fascial planes) more easily and rapidly spread than those arising within a muscular compartment.

Our results support those of Sørensen et al,²¹ who found that an intercompartmental (that is, fascial) location of DTs, determined during surgery in 72 patients, was an independent poor prognostic factor in patients with DT.

Our results also agree with the only previous effort (to our knowledge) at determining MRI-based prognostic factors in DTs³¹ in that we did not find an association between EFR and imaging features that are thought to represent tumour aggressiveness (Figure 4).

Similar to other investigators,^{9,10,12-15} we did find an association between EFR and tumour location, with tumours in the limb associated with worse outcome on univariate analysis; however, this association was not preserved as an independent prognostic factor on multivariate analysis (Table 2).

Our results showed that chemotherapy alone or “other treatment” were independent positive prognostic factors for EFR compared with surgery alone in a multivariable model including location and compartment of origin. However, the chemotherapy-alone group included a diverse set of therapies ranging from conventional/cytotoxic to hormonal and tyrosine kinase inhibitors, either alone or in combination (Table 1), and the “other” group included various combinations of chemotherapy, radiation therapy and surgery. In addition, patients were not randomized between treatment modalities and any comparisons without accounting for the probability of receiving these treatments would be highly biased.³⁴ Therefore, conclusions about optimal therapy should not be inferred from our results.

In contrast to previous efforts at deriving prognostic factors from genetic, histopathological and clinical variables,^{6,9-20,22-25} we did not find an association between age, sex, resection margins and *CTNNB1* mutation status. This last variable deserves special note. The 47 patients in our study with *CTNNB1* mutation analysis represents a subset of data previously published, which showed that tumours with p.S45F mutations were associated with worse prognosis compared to wild-type or other mutations (p.S45P and p.T41A).^{22,23} It is

Table 2. Selected univariate and multivariate analysis for association with time to event (recurrence or progression)

Characteristic	<i>n</i>	Selected univariate			Selected multivariable		
		HR	95% CI	<i>p</i> -value	HR	95% CI	<i>p</i> -value
Age (every 1 year)	90	0.99	0.97–1.01	0.42			
Sex	90						
Female		0.89	0.48–1.64	0.7			
Male		–	–	–			
Treatment	88						
Other		0.39	0.18–0.86	<i>0.0195</i>	0.28	0.12–0.65	<i>0.0029</i>
Chemo only		0.32	0.1–1.06	0.06	0.28	0.08–0.98	<i>0.045</i>
Radiation only		0.49	0.15–1.61	0.24	0.38	0.11–1.27	0.12
Surgery only		–	–	–	–	–	–
Resection margins	60						
Positive		0.89	0.46–1.71	0.72			
Close/negative		–	–	–			
Mutation status	47						
p.S45F		0.77	0.30–2.01	0.6			
Other		–	–	–			
Location	89						
Limb		2.23	1.19–4.14	<i>0.0123</i>	1.56	0.08–3.02	0.19
Trunk		–	–	–	–	–	–
Depth	90						
Superficial		0.82	0.32–2.10	0.68			
Deep/both		–	–	–			
Compartment of origin	89						
Fascial		3.2	1.57–6.52	<i>0.0014</i>	3.9	1.83–8.32	<i>0.0004</i>
IM/SC		–	–	–			
Confined to compartment	90						
No		0.68	0.29–1.62	0.37			
Yes		–	–	–			
Dominant shape	90						
Infiltrative		1.23	0.68–2.23	0.50			
Round/oval/lobulated		–	–	–			
Dominant margin	90						
Indistinct		1.23	0.68–2.23	0.50			
WD/pseudocapsule		–	–	–			
Size (every 1 cm)	90	1.43	0.79–2.59	0.24			

Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; IM, intramuscular; SC, subcutaneous; WD, well defined; –, reference for regression analysis.

Italicized values indicate statistical significance (<0.05).

important to stress that because our inclusion criteria (presence of pre-therapy MRI) introduced a selection bias, it cannot be used to confirm or invalidate the results of the original study, which included a larger number of patients.

Our study has several limitations. Most importantly, it was a retrospective study with a diverse set of treatment modalities that were selected on a case-by-case basis based on various subjective, clinical and patient variables. A prospective study,

Figure 5. Kaplan-Meier curves for event-free rate for the different compartments of origin. (a) Time to event (recurrence or progression) differed significantly for the four compartments of origin ($p = 0.002$). (b) Time to event differed significantly for compartment of origin when grouped as intramuscular/subcutaneous (IM/SC) vs superficial/deep fascial (SF/DF) ($p < 0.001$).

with uniform selection criteria will be needed before the results can be confidently generalized. A further limitation inherent to a retrospective study is the selection bias introduced because of exclusion of the majority of extra-abdominal desmoid tumours. From a total of 406 extra-abdominal DTs, only 90 (22%) met inclusion criteria. The majority of the excluded patients (259 or 64%) lacked pre-therapy MRI (owing to the absence of imaging in the setting of unplanned excision, inability to obtain pre-therapy MRI or the use of CT or ultrasound for pre-therapy imaging).

Another limitation is related to the nature of image review in this study, which is not how radiology studies are interpreted in clinical practice. A validation study with multiple readers will be needed to assess the inter- and intrareader variability of the classification system and its applicability to clinical practice.

CONCLUSION

We have shown that IM or SC DTs are associated with improved EFR, whereas other imaging features commonly associated with biological behaviour (e.g. shape, margins, T_2 signal and enhancement) are not. If validated on multireader and prospective studies, these results can provide for rapid risk stratification of patients at the time of initial MRI. Future work will be needed to determine if compartment of origin can serve as an imaging biomarker for tumour aggressiveness and allow for selection of patients for observation.

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