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EDITORIAL – SARCOMA

If Active Surveillance is the Standard of Care for Desmoid Patients, When Should Intervention be Considered?

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In this issue, experts at Royal Marsden Hospital report the outcomes for a large cohort of patients with desmoid tumor (DT) who did not undergo intervention at the time of their initial diagnosis.[1] In the management of DT patients, understanding in whom to intervene and when are seminal questions that are not yet resolved. What has been clarified in DT clinical care is that the need for upfront surgery has evolved, at most, to second-line consideration after a period of observation.[2] In this vein, the current report describes 584 DT patients during an 18-year period, 168 of whom were managed with active surveillance. Most of these patients did not need any form of additional treatment during the follow-up period. The main indications in those treated were tumor progression, pain, or both, which occurred within 2.5 years after diagnosis.

Desmoid tumors (also known as desmoid-type fibromatosis) are rare mesenchymal neoplasms of fibroblastic derivation that can be locally invasive, but have no metastatic potential. They occur with an annual incidence of 2–4 per 1,000,000 individuals and tend to develop in younger patients. Most DTs arise sporadically, although some may be associated with trauma or pregnancy. In addition, DTs occur in patients who have familial adenomatous polyposis (FAP), developing in 10–20% of these patients. Intriguingly, spontaneous regression has been reported in 19–28% of all DT cases,[3,4] which is seen predominately in abdominal wall DT. Furthermore, active surveillance—defined as establishing the diagnosis of DT, performing serial imaging (MR, CT, and /or US) with patient evaluation every 3–6 months, to determine if the tumor may require intervention, has been adopted as primary standard of care by the majority of expert centers over the past 5–10 years.

Actively observing patients and avoiding unnecessary intervention with surgery, radiation, and/or drug therapy has enhanced our knowledge of DT biology as we increasingly appreciate that the majority of patients in fact do not require specific treatment for this benign condition. However, our ability to stratify which patients will have more aggressive biology is not well established. A significant limitation of the current retrospective series was the inherent selection bias encompassing the patients observed versus those not observed. Nonetheless, this seminal study from the Royal Marsden provides further credence that active surveillance should be the frontline approach in sporadic DT as only 46% of the patients progressed and/or symptomatically required intervention.

Active surveillance dominated this large series, especially in the latter part of the study period. Indications for upfront surveillance in this series included: no/limited symptoms, slowly growing tumor, no involvement of relevant structures, and/or patient preference. The Royal Marsden cohort was composed of young patients (median age, 42.2 years; range, 11–86 years) with a median tumor size of 5.9 cm and included all disease sites [abdominal wall (36%), extremity (30%), chest wall (18%), intrabdominal (9%), and other (6%)]. Overall, 36% of the patients progressed (most commonly in the upper extremity

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and chest wall), 36% remained stable, and 27% had partial or complete regression, in keeping with outcomes of initial observation in other institutional series.[4–6]

Although first-line active surveillance is definitely more globally accepted, decision making related to the timing of intervention for DT patients undergoing observation is not as well defined. Thus, the central premise of this article is to evaluate factors that correlate with tumor behavior and/or the need to intervene after initial surveillance. The only variable that univariate analysis identified with disease progression was age younger than 50 years at diagnosis (Table 2[1]). Previous studies identified young age as correlated with increased recurrence after DT surgery, but exactly why tumor biology varies across the age spectrum has not been resolved to date.[3,7] In contrast, variables associated with intervention after a period of observation shown by multivariable analysis were: size ($\geq$ 7 cm; $p < 0.05$; hazard ratio [HR], 1.8; range, 1.1–2.8), pain ($p < 0.01$; HR, 2.1; range, 1.3–3.3), stable disease ($p < 0.01$; HR, 2.1; range, 1.3–3.3), and most strikingly, tumor progression ($p < 0.01$; HR, 10.5; 4.1–26.7) (Table 3[1]). Although site also was not statistically significant for intervention, the majority of upper-extremity (58%) and chest wall (57%) patients required treatment (Figure 1[1]), consistent with their clinically appreciated aggressive biology.[5] Intriguingly, the median time to the initiation of any treatment was 6.5 months, which, possibly, was somewhat soon. Early intervention may explain why stable disease was associated with intervention in this cohort of DT patients who were mostly asymptomatic. Clearly, future studies on prospective decision making will help to illuminate how long one should wait before intervening and which variables are key in driving clinician and patient agreement to proceed with treatment.

The type of treatment used after the decision to treat DT patients evolved during the period of this study as initially, surgical intervention dominated. However, this decreased to 20% of all interventions over time as indications were refined to keep abdominal wall disease or emergency intervention for symptomatic abdominal patients. Although elective surgery has been largely discouraged for sporadic desmoids, additional considerations include progressing mesenteric disease that may pose a significant risk of vascular involvement and/or patients who cannot engage in an active surveillance program for more favorable sites such as the abdominal wall.

Following methotrexate plus vinca agent chemotherapy,[8] systemic therapy for DT has remained enigmatic, but possibly more sophisticated and convenient. Pazopanib, sorafenib, and possibly gamma-secretase inhibitors offer patients oral therapy with excellent opportunity for disease control.[9,10] All studies to date have been limited, however, in reporting the optimal duration of therapy. Should the bar to intervene for an individual with DT possibly be different if an oral therapy is being considered rather than surgery or radiation? In the study by van Houdt et al., the indications for therapy and the type of systemic therapy offered were unfortunately not described. Finally, the use of radiation therapy (RT) for this benign condition is decreasing. At the University of Toronto, RT is limited to those with medically refractory DT in which surgery would be exceedingly morbid. Regardless, multidisciplinary evaluation is warranted so the ideal opportunity for comprehensive, patient-centered care can be offered to all DT patients.

The lack of intervention described by van Houdt et al. truly is a dogma that has been embraced. However, one wonders about the emotional impact on patients to continue returning on a regular basis to a (cancer) center for ongoing CT or MRI scans and follow-up assessment with an oncologic provider.[11] Recently, we reported higher levels of anxiety in individuals with DT even compared with sarcoma, which in fact did not ease with treatment, and continued throughout surveillance. At our center, we have the tools to offer routine distress and symptom screening for all patients—however screening falls short unless resources are available to aid in treating patient anxiety. In a culture of active surveillance, treatment for anxiety, distress, and symptoms still needs to be addressed.

In summary, we applaud the expert multidisciplinary team at the Royal Marsden Hospital for compiling the largest retrospective review of patients with DT who have undergone active surveillance, increasing our collective confidence in observing these patients. The community should continue to understand the impact of surveillance on patients and coordinate prospective data collection to clarify the triggers for intervention and identify biologic factors prognostic for tumor progression. With this precision, we may be able to refine risk stratification further and tailor the frequency of surveillance and counseling for the lowest- and highest-risk DT patients.

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