

Clinical and genomic characterization of desmoid fibromatosis

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Desmoid fibromatosis

- Locally aggressive tumor without metastatic potential.
- Associated in 85% of patients with mutation in *CTNNB1* gene, rarely in context of Gardner's syndrome.
- Historically treated with surgery though high rates of local recurrence were reported (25-50%).
- Radiation has been considered in the adjuvant setting, but rarely used now.
- Now have options of:
 - Chemotherapeutics like sorafenib or Doxil
 - Observation



Clinical questions in management of desmoid fibromatosis

- How do we counsel patients?
 - Who is most likely to progress during an initial period of observation?
 - Who are best candidates for surgical versus medical management?
- Are clinical and pathologic factors sufficient to predict outcomes or can molecular characteristics improve models?



***Who are best candidates for
surgical versus medical
management?***



Outcomes after desmoid resection

- 495 patients underwent surgical resection of a desmoid tumor.
- Between 1982 and 2011.
- Median follow-up 60 months.
- Longest follow-up 327 months.

Characteristic	Primary (n=382)	Recurrent (n=113)	p-value (univariate)
Gender			0.734
Male	130 (34%)	36 (32%)	
Female	252 (66%)	77 (68%)	
Age			0.074
15-25y.o.	67 (18%)	28 (25%)	
26-45y.o.	183 (48%)	61 (54%)	
46-65y.o.	92 (24%)	18 (16%)	
>65y.o.	39 (10%)	7 (6.2%)	
Location			<0.001
Abdominal wall	77 (20%)	11 (9.7%)	
Chest wall	50 (13%)	26 (23%)	
GI/Intraabdominal	94 (25%)	6 (5.3%)	
Extremity	116 (30%)	61 (54%)	
Other	45 (12%)	9 (8.0%)	
Depth			0.914
Superficial	28 (7.3%)	7 (6.2%)	
Deep	351 (92%)	105 (93%)	
Unknown	3 (0.79%)	1 (0.88%)	
Margin			0.05
R0	216 (57%)	51 (45%)	
R1	130 (34%)	43 (38%)	
R2	35 (9.2%)	18 (16%)	
Unknown	1 (0.26%)	1 (0.88%)	
Size			<0.001
<=5cm	112 (29%)	36 (32%)	
>5cm, <=10cm	155 (41%)	45 (40%)	
>10cm	113 (30%)	12 (11%)	
Unknown	2 (0.5%)	20 (18%)	
FAP	11 (2.9%)	4 (3.5%)	



Post-operative outcomes

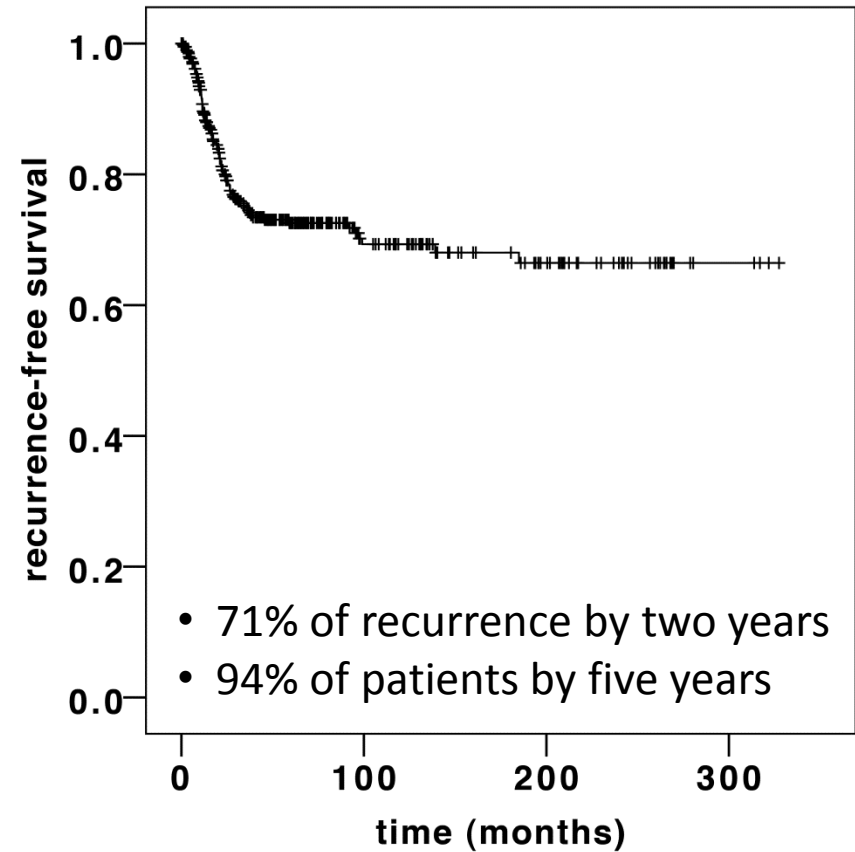
90% underwent complete gross resection

More likely to have R2 resection if:

- >10cm
- Abdominal tumor
- FAP

Five year RFS 71%

Recurrence free survival R0/R1

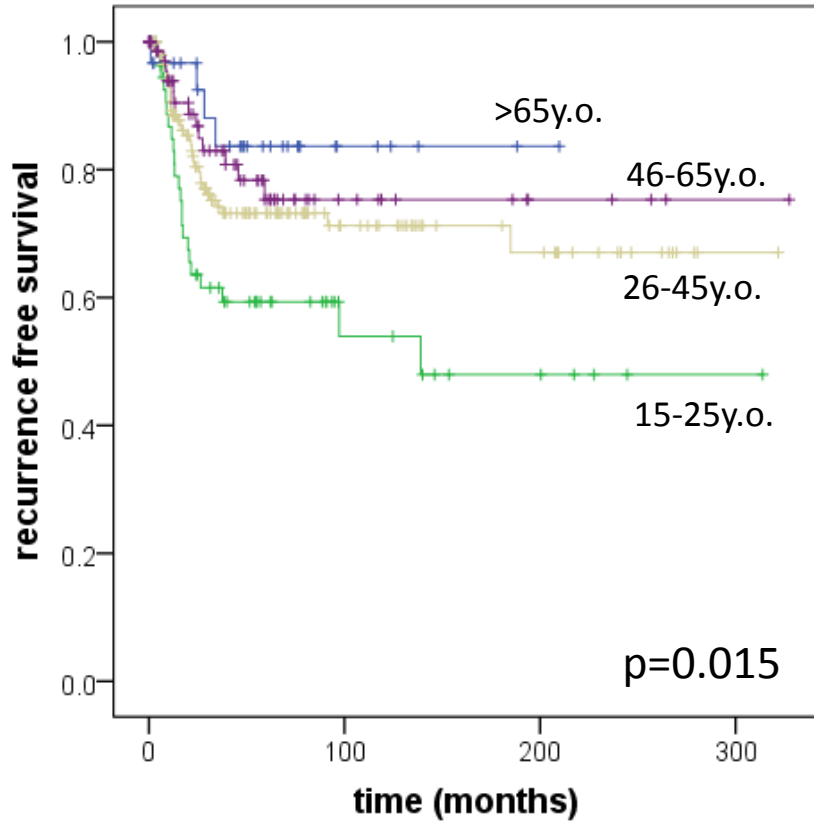


Very few patients died after desmoid resection

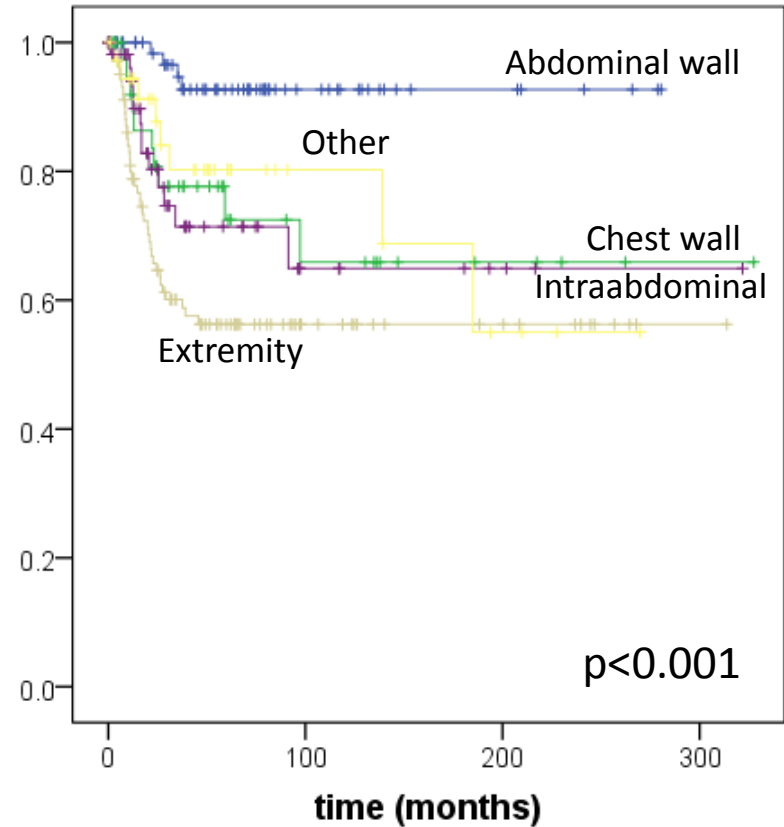
Age	Gender	Year of surgery	Site	Margin	
16y.o.	M	2001	Intraabdominal	R2	Gardner's disease, died 5 yrs. s/p intestinal transplant
45y.o.	M	1983	Intraabdominal	R2	Intraabdominal treated with surgery and RT, details of death unclear
43y.o.	M	1974	Intraabdominal	R2	H/o metastatic testicular cancer treated with surgery and chemo complicated by cardiac failure, subsequent intraabdominal desmoid.
29y.o.	M	2007	Intraabdominal	R2	Died in hospice after attempt at small bowel transplant
21y.o.	F	1996	Paraspinal	R2	Gardner's syndrome, rapid increase in tumor size with high narcotic requirement
62y.o.	F	2001	Base of skull	R2	Progression on chemotherapy
43y.o.	M	1974	Mediastinum	R2	Died of pneumonia in context of progressive, chemo-resistant disease

Clinical characteristics and outcome in primary desmoids

Age and recurrence

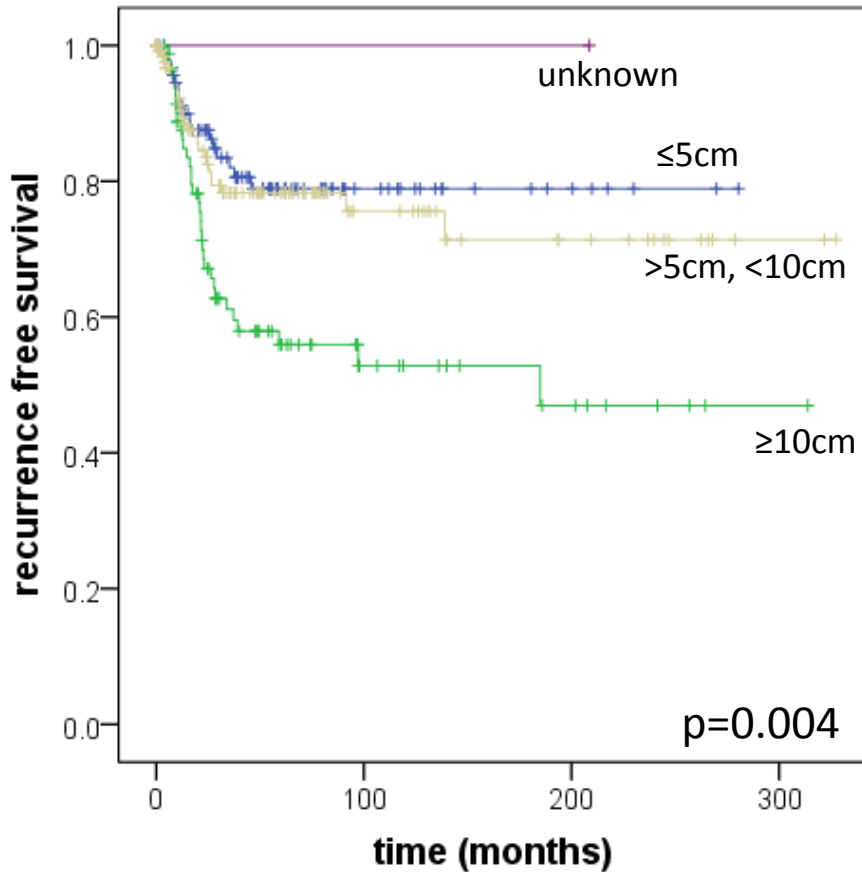


Site and recurrence

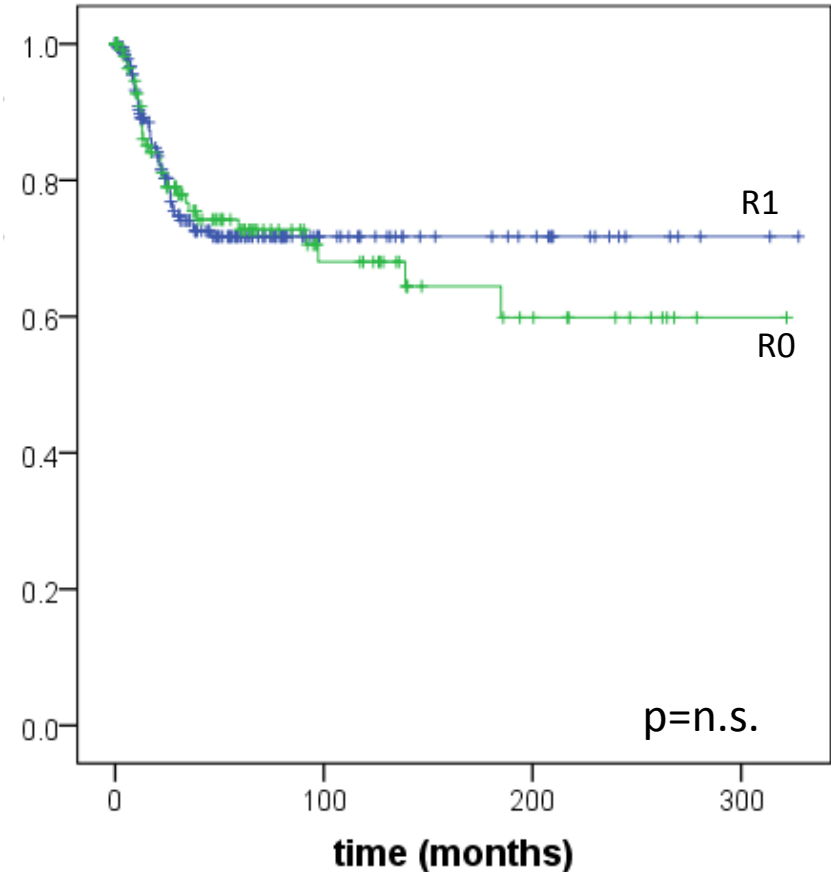


Clinical characteristics and outcome in primary desmoids

Size and recurrence



Margin and recurrence



No affect seen when stratified by:

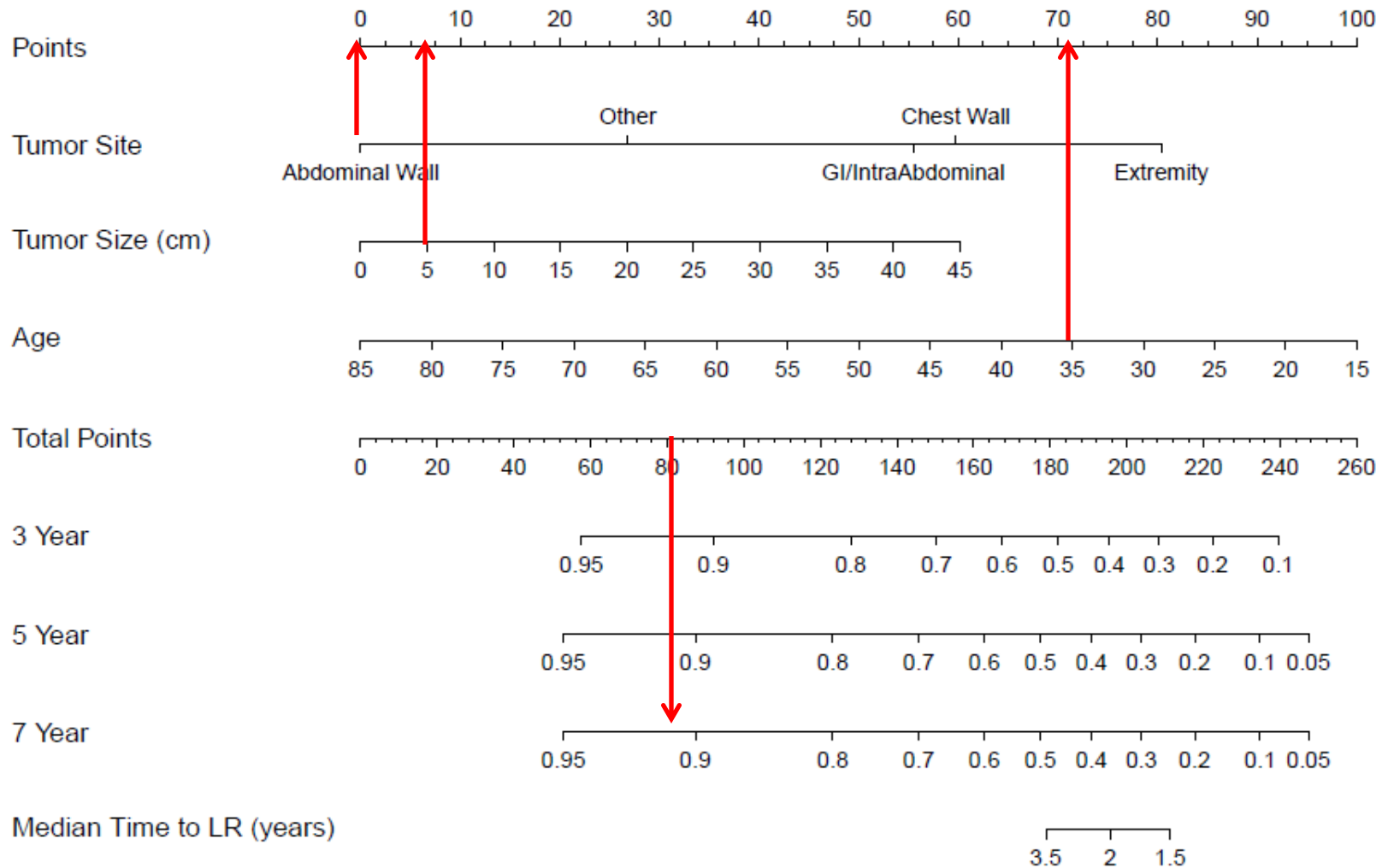
- Gender
- Presentation status (primary vs. recurrent)



Clinical characteristics and outcome – multivariate analysis

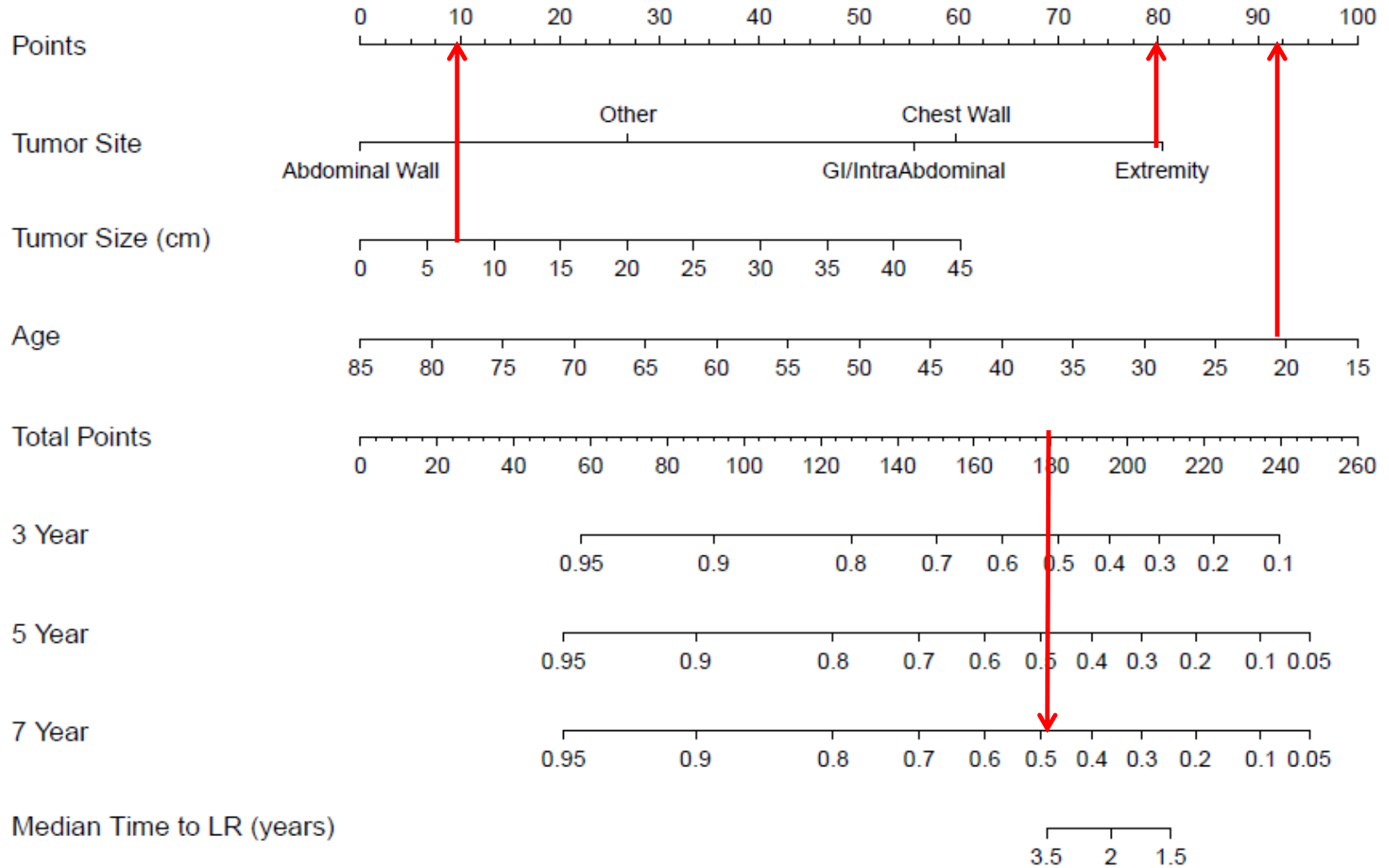
Factor	Hazard ratio (95% confidence interval)	p-value
Margin status (R1 vs. R0)	1.01 (0.66, 1.56)	0.96
Presentation status (recurrent vs. primary)	1.15 (0.70, 1.89)	0.59
Depth (deep vs. superficial)	1.44 (0.56, 3.67)	0.45
Gender (female vs. male)	1.30 (0.82, 2.09)	0.26
Primary site (vs. abdominal wall)		
Extremity	5.09 (2.17, 11.9)	<0.001
Chest wall	3.13 (1.18, 8.32)	0.022
Intraabdominal	2.72 (0.98, 7.56)	0.054
Other	1.50 (0.30, 7.49)	0.62
Primary size (vs. <5cm)		
5-10cm	0.82 (0.46, 1.46)	0.50
>10cm	1.69 (0.93, 3.07)	0.086
Age (vs. <25y.o.)	1.00	
25-65y.o.	0.57 (0.37, 0.89)	0.013
>65y.o.	0.29 (0.099, 0.83)	0.021

**Prognosis in abdominal wall desmoids –
A nomogram to predict post-operative recurrence**



*** A 35 y.o. woman with a small, rectus sheath desmoid has <10% chance of recurring after surgery based on the nomogram**

Prognosis in extremity desmoids



*** Risk is much higher for a young patient with a large, extremity lesion**

External validation of desmoid nomogram

Outcomes of 426 patients in European database analyzed by Salas *et al.*

Risk factors for progression and recurrence:

- Size
- Patient age
- Tumor location

Created a three point risk stratification schema.

External validation of the nomogram performed on subset of these patients having undergone R0 or R1 resection of a desmoid.

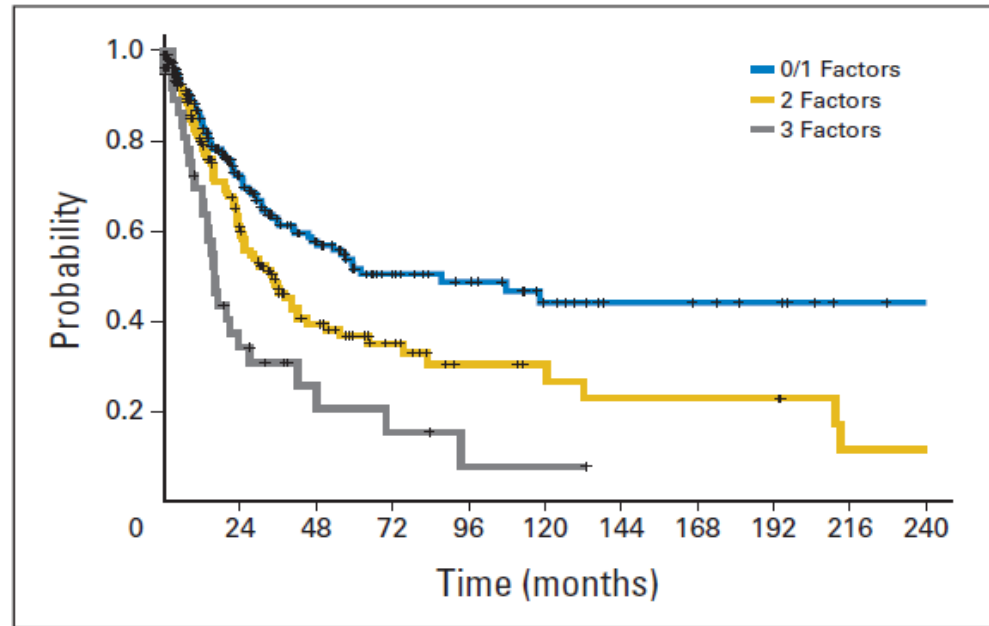


Fig 2. Probability of survival of patients with zero, one, two, or three factors.

Comparison of nomogram & three point system – relative concordance indices

	MSKCC	French data
Nomogram	0.703	0.659
Three point system	0.532	0.570

Conclusions

- Clinical risk factors can predict recurrence after surgical resection.
- A nomogram which calculates risk of local recurrence following surgical resection of desmoids can assist clinicians in counseling patients.
- Patients with large, extremity tumors have a high risk of local recurrence and may benefit from systemic treatments as first line therapy as compared to those with abdominal wall tumors who are almost always cured with surgery.
- Future studies will examine the role of genetic markers in improving our ability to predict risk of post-operative recurrence.

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