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# If your lump is bigger than a golf ball and growing, think Sarcoma

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## Abstract

*Aim*: Only 1 in 100 of primary care consultations regarding new soft tissue lumps (STL) are malignant and are susceptible to a delay in diagnosis. We aimed to generate a Bayesian Belief Network to estimate the likelihood of malignancy in patients to facilitate the initial evaluation of a STL and improve timing and quality of referrals to specialist treatment centres.

*Methods*: We evaluated all patients referred with a new STL between 1996 and 2007. Variables investigated focused on patient factors, symptoms and STL characteristics. Relevant data was extracted and coded for statistical analysis.

*Results*: 3018 patients with a STL were assessed, of which 1563 (52%) were benign and 1455 (48%) malignant. The features most conditionally associated with the outcome of interest (Benign or Malignant) are referred to as first-degree associates, and are increasing size, age, size of the lump, and duration of symptoms, in that order. On cross validation, this model demonstrated an AUC of 0.77 (95%C.I. 0.75–0.79).

*Conclusions*: For the first time, we have described the hierarchal relationship between factors and created an aide memoire, larger than a golf ball and growing, to trigger referral to tertiary tumor units. Importantly, we found pain to be a poor discriminatory factor. We hope our findings will lead to greater awareness and earlier diagnosis of STL.



*Keywords:* Golf ball; Sarcoma; Nomogram; Soft tissue lump; Bayesian belief network

## Introduction

Primary care consultations regarding new soft tissue lumps (STL) are common, however only 1 in 100 of these are malignant,[1] for every malignant soft tissue tumour of any type examined by a pathologist, there are at least 100 benign soft tissue masses.[2] Hence, STL provide a diagnostic challenge for General Practitioners when identifying the infrequent but crucial diagnosis of Soft Tissue Sarcomas (STS). STS are complicated by the fact that they represent at least 80 potentially malignant histological types and subtypes.[3] Not only are they rare, STS are a diverse group of malignancies with variable presentation, behaviour and outcomes.[3]

In 2010 there were 3298 new diagnoses of STS in the UK,[4] with an incidence of 45 per million,[4] which is rising. In an average general practice of 3000 patients, at least three cases of benign soft tissue tumour per year can be expected. However, only one case of soft tissue sarcoma would be expected in this population every 24 years.[5] Inexperience in primary care can lead to delayed referrals or inappropriate treatment such as inadvertent excision.[6,7] A number of studies have attributed these delays in referral to health professionals in primary and secondary care.[7,8]

Delay in diagnosis is important and may lead to significantly poorer patient outcomes. Late diagnosis leads to an increased size at presentation, greater incidence of metastasis at presentation and poorer resection margins, greater amputation risk and greater risk of surgical complications.[9,10] The natural history of STS has prompted efforts to increase public awareness and increase efficiency of

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referral pathways. Guidelines were published in 2000 and 2005 instructing urgent referral (2 week pathway) for a patient with a soft tissue mass with any one of the following features: size >5 cm; increasing size; deep to fascia; painful; recurrence.[11,12] There have been modest improvements in 5-year survival with rates increasing from 51% in 1996–2000 to 55% in 2006–2010.[13] Despite a 25-fold increase in 2-week wait pathways we are not seeing improvement in early diagnosis or mean size at presentation.[14,15]

## Aims

In an earlier article, Size Matters for Sarcoma,[10] the senior author suggested that a golf ball would be a good aide memoir to prompt referral of soft tissue lumps. This study will generate clinical decision support model to estimate the likelihood of malignancy in patients referred for evaluation of their STL, demonstrate the conditional relationships between variables (features) suggestive of malignancy and analyse the predictive value of size compared to a golf ball (4.3 cm). Following internal validation these characteristics will be recommended as Red Flag referral criteria for clinicians to implement and enhance referral pathways to specialist cancer centres, whilst minimising inappropriate treatment of STL.

## Methods

All consecutive patients referred to the Royal Orthopaedic Hospital for assessment of a STL between 1996 and 2007 were included. STL were identified from our single institution's prospectively maintained database. Our unit is a tertiary referral centre serving a population of around 5 million for STS patients, therefore referrals of suspected malignant soft tissue lumps were received from both primary and secondary care, based either on clinical criteria alone (2 week wait) or, from hospitals often following prior investigation with supplementary imaging or biopsy in some instances. Patient details and clinical information gleaned at the initial clinic appointment were entered onto the database. A previous study details the origin of referrals to our regional Sarcoma unit, with 16.4% being via two-week wait criteria and these had a 13% malignancy rate (Taylor et al., 2010).

The features extracted for statistical analysis included: size of mass (cm); location of lump (superficial or deep to fascia); lump growing (yes or no); painful (yes or no); patients age (years); duration of symptoms (weeks); anatomic location; final histological diagnosis (benign or malignant). Missing data was acceptable, however, records containing less than 2 features were excluded from the study.

Symptom duration was defined as the patient's subjective recollection of the duration of symptoms (DOS) in weeks prior to their first clinic attendance. STL were divided by location, into superficial or deep tumours relative to deep fascia. For analysis purposes STL size was recorded as the maximum dimension in any plane in centimetres at the time of assessment. Most patients had some form of imaging and the size was based on either MRI or ultrasound results, or, if neither of these was done, then on clinical examination findings. Patients were subdivided into two groups based on whether their lump was greater or less than 4.3 cm (the size of a golf ball).

We compared the presence of these individual features with the eventual histological diagnosis. Comparing the prevalence of features in patients with benign or malignant lumps. Preliminary statistical analysis was carried out using IBM SPSS Statistics Version 20. Statistical methods for nonparametric data, such as duration of symptoms used Mann–Whitney U Test with a predetermined P-value of $<0.05$. Nominal data was assessed using odds ratio and chi-square analysis to infer differences in prevalence of features.

In order to represent the relationships between features, and to estimate the likelihood of malignancy, we developed a Bayesian Belief Network (BBN). The BBN model was developed in a manner similar to that previously described,[16] using commercially available machine learning software (FasterAnalyticsTM; DecisionQ, Washington, DC, USA). Briefly, all features were considered as candidate features for inclusion in the model. Prior to modelling, missing data for each feature was imputed using a passive imputation algorithm. We used an equal-area binning process for continuous features, based on prior distributions learned from the training set. Two models were developed: one considering tumour size as a continuous variable binned into five categories, using an equal area binning process, and one considering size as $\pm 4.3$ cm, the dimensions of a golf ball. Ten-fold cross validation was performed, and the Area Under the Receiver Operator Characteristic (ROC) curve (AUC) generated. In addition, lift analysis was performed on each first-degree associate to determine the relative contribution of each with respect to accuracy. Briefly, the increase in AUC was calculated after adding, each first-degree associate, in turn, to a model containing only second-degree associates.

## Results

In total, 3018 lumps were analysed in this study. 1563 (52%) were benign and 1455 (48%) were malignant. The frequency of benign and malignant conditions graded by each of the clinical features is shown in Table 1.

The mean age of patients with benign lumps was younger than those with malignant lumps (46 vs. 56 years $p < 0.001$). Patients with malignancy also reported shorter median duration of symptoms (26 vs. 32 days $p < 0.001$) than larger lumps (Table 2). It is evident that the greater number of positive features at presentation the greater the risk of malignancy. (Fig. 1).