**ONCOLOGY**

The effect of surgical synovectomy and radiotherapy on the rate of recurrence of pigmented villonodular synovitis of the knee

**AN INDIVIDUAL PATIENT META-ANALYSIS**

Pigmented villonodular synovitis (PVNS) is a rare proliferative process of the synovium which most commonly affects the knee and occurs in either a localised (LPVNS) or a diffuse form (DPVNS). The effect of different methods of surgical synovectomy and adjuvant radiotherapy on the rate of recurrence is unclear. We conducted a systematic review and identified 35 observational studies in English which reported the use of surgical synovectomy to treat PVNS of the knee.

A meta-analysis included 630 patients, 137 (21.8%) of whom had a recurrence after synovectomy. For patients with DPVNS, low-quality evidence found that the rate of recurrence was reduced by both open synovectomy (odds ration (OR) = 0.47; 95% CI 0.25 to 0.90; p = 0.024) and combined open and arthroscopic synovectomy (OR = 0.19, 95% CI = 0.06 to 0.58; p = 0.003) compared with arthroscopic surgery. Very low-quality evidence found that the rate of recurrence of DPVNS was reduced by peri-operative radiotherapy (OR = 0.31, 95% CI 0.14 to 0.70; p = 0.01). Very low-quality evidence suggested that the rate of recurrence of LPVNS was not related to the surgical approach.

This meta-analysis suggests that open synovectomy or synovectomy combined with peri-operative radiotherapy for DPVNS is associated with a reduced rate of recurrence. Large long-term prospective multicentre observational studies, with a focus on both rate of recurrence and function, are required to confirm these findings.

Cite this article: Bone Joint J 2015;97-B:550–7.

pigmented villonodular synovitis (PVNS; also termed tenosynovial giant cell tumour) is a rare synovial proliferative disease. It is unclear whether it is the result of a neoplastic or an inflammatory process. Histologically, it is characterised by the presence of inflammation, haemosiderin deposition, multinucleate giant cells and lipid-laden macrophages. It often presents in a monoarticular form and can involve any structure lined with synovium but its most common intra-articular site is the knee. PVNS is either localised (LPVNS), when it presents as a solitary pedunculated lesion, most frequently in the anterior compartment of the knee, where it is surrounded by normal synovium; or diffuse (DPVNS), when it involves the whole joint and is villous in nature.

PVNS is considered a benign, locally aggressive process which, if left untreated, can lead to joint destruction and osteoarthritis (OA). Whereas marginal excision of LPVNS is considered adequate for long-term control, DPVNS requires extensive resection and still may result in a high rate of local recurrence. Adjuvant external beam or intra-articular radiotherapy may also be used to help gain local control. Patients with many recurrences or refractory disease leading to OA may need joint replacement.

Surgical resection, either open or arthroscopic, is considered the mainstay of treatment for PVNS of the knee. Although good to excellent functional results have been reported using both techniques, both have their limitations. Open surgery, potentially using a combination of anterior and posterior incisions, is associated with a longer hospital stay, a prolonged period of rehabilitation and potential post-operative stiffness or wound complications. An arthroscopic synovectomy is thought to accelerate healing and reduce complications, but considerable technical expertise is needed to achieve complete excision. Furthermore, large popliteal masses or extra-articular involvement are not amenable to arthroscopic excision. Combined arthroscopic and open procedures may achieve complete excision while mitigating the risks and limitations of both procedures, but there is little objective evidence to support this view.

The rarity of PVNS virtually precludes the use of randomised controlled trials to assess
the effect of the various therapeutic approaches, and only observational studies have been feasible. Many existing reviews of the literature include clinical data from the prearthroscopy era. Consequently, the rates of recurrence that are reported in older studies may not reflect current clinical practice. No previous studies have explored how the rate of recurrence is influenced by the use of different surgical techniques (open, arthroscopic, combined) or the addition of radiotherapy, nor have reviews attempted to pool results across studies.

In order better to understand the effect of modern surgical approaches and radiotherapy in the treatment of PVNS of the knee, we conducted a systematic review and an individual participant meta-analysis (IPMA) and report our findings in concordance with the PRISMA21 and MOOSE22 guidelines. We hypothesised that open procedures would be associated with a lower rate of recurrence but a higher rate of complications than arthroscopic or combined open/arthroscopic approaches. We further hypothesised that the addition of radiotherapy would be associated with a reduced rate of recurrence but a higher rate of complications.

Materials and Methods
Two reviewers (BM, AL) independently identified relevant case series or observational studies published in English, by systematically searching MEDLINE and EMBASE between 1 January 1981 and 31 December 2012, using the search terms ‘pigmented villonodular synovitis’ and ‘tenosynovial giant cell tumour’. We selected 1981 as the earliest date of publication in order to reflect more contemporary surgical and radiotherapeutic treatment. Reviewers scanned the bibliographies of all retrieved studies for additional relevant articles. All eligible studies were ‘forward searched’ through MEDLINE, EMBASE and Google Scholar to identify additional publications that cited eligible studies.

Eligibility criteria. Two reviewers (BM, AL) with content and methodological expertise screened the titles and abstracts independently and in duplicate and acquired the full-text publication of any article that was judged potentially eligible. The same reviewers independently applied eligibility criteria to the methods section of potentially eligible trials. Eligible trials met the following criteria: they described observational studies of patients with PVNS of the knee treated by synovectomy; they reported the rate of recurrence of PVNS; and they reported data in the manuscript or data provided by the authors that allowed meta-analysis to be undertaken. We excluded case reports. Disagreements were resolved by discussion.

Data abstraction. One of the reviewers (BM or AL) extracted data independently from each eligible study: all extracted data were confirmed by the other reviewer. Data abstracted included demographic information, methodology, details of interventions rates of recurrence, postoperative stiffness, the need for reoperation or arthroplasty, and complications.

Assessment of study quality. Because of the inherent limitations and risk of bias with case series, as well as the clinical heterogeneity presumed to exist between series, all trials were considered to have a ‘serious to very serious’ risk of bias for the purpose of our pooled quality of evidence measures (discussed below). No validated screening tool was felt to be applicable to these studies and so individual studies were not assessed for quality. We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) evidence profile21,22 to evaluate the confidence in evidence for predicting recurrence of PVNS. We rated confidence in evidence using GRADEpro software, version 3.6 (the Cochrane Collaboration).

Statistical analysis. For continuous data, we reported the mean and standard deviation (SD) or the range. For dichotomous outcomes we reported frequencies and percentages. Chi-squared analysis was performed for dichotomous outcomes, where appropriate, and was reported with 95% confidence intervals (CI) and p-values. We set the α level for statistical significance at 0.05.

IPMA is recognised as the best method of conducting pooled analysis.23 It allowed us to address questions not addressed in the original publications, such as the determination of predictors of outcomes in a study that had an alternative objective; to use common definitions, coding and cut-points; to ensure the accuracy of aggregated study data; to account for the variability in follow-up times; and to enhance the statistical power of identifying treatment variables associated with recurrence.

When data were available for individual participants, we conducted multivariable logistic regression analysis (IPMA) for LVPNS and DPVNS patients to explore the association between the type of surgical approach and the use of radiotherapy with recurrence of PVNS at the longest follow-up time reported. Patients were classified as having received one of two forms of radiotherapy: external beam or intra-articular. Due to limitations in sample size, we were unable explore any differences between these two groups, and so both were grouped together as receiving ‘peri-operative adjuvant radiotherapy’. The administration of radiotherapy was classified as ‘peri-operative adjuvant radiotherapy’ or ‘no/unplanned/delayed radiotherapy’. Radiotherapy was considered ‘peri-operative’ if it was undertaken within three months of surgical synovectomy and was not used to treat a recurrence that developed after surgery. For example, radiotherapy was considered ‘peri-operative’ if it was used to treat residual disease that was not resectable at the time of arthroscopy, regardless of the patient’s symptoms. Conversely, radiotherapy used to treat recurrent disease, or residual disease that progressed to become symptomatic after an initial period without symptoms, was considered to be ‘delayed’. Studies where this information was not reported in a manner that allowed for the extraction of data about individual participants, and where the authors could not be reached for clarification, were excluded from our IPMA but are described in the review. We adjusted for the

VOL. 97-B, No. 4, APRIL 2015
study effect in each model, which we entered as a random effect. IPMA analysis was performed using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina). We reported our findings using odds ratios (OR), 95% CIs and p-values.

**Results**

We identified 1392 unique citations from our electronic search. After screening the titles and abstracts, as well as the bibliographies of relevant reviews, and forward-searching articles published before 1981, 60 articles were reviewed in full (Fig. 1). The authors of six separate trials were approached to clarify data,14,19,24-27 of whom four responded.14,24,26,27 Additional data were provided for two studies,24,26 and the remaining correspondence helped to answer general questions and clarify the published data. Two studies were ultimately excluded as detailed below due to insufficient data27 or difficulty in obtaining contact with the author.19

In all, 21 reviewed citations were excluded as they were published before 1981. Five studies were excluded because the structure of the article was more in keeping with a case report, despite commenting on many patients.28-32 Three articles were not published in English;13-33 three did not separate the results of PVNS of the knee from those of other sites and the available data precluded useful knee-specific data extraction;19,36,37 three focused on radiotherapy and/or failed to mention the preceding surgical procedure;38-40 two focused on extra-articular giant cell tumours and their pathology;41,42 one focused on the treatment of metastatic PVNS;43 one focused on imaging of PVNS with no long-term surgical outcomes;44 and the patients of three studies45-47 were thought to have been included in three other studies,14,18,25 given the similarities in the patient population across the same centres and the period of the research. Additionally, the reporting in four studies15,27,48,49 precluded the extraction of data about individual patients and the authors could not be contacted for clarification.

Therefore, 35 studies reporting on 630 patients with PVNS of the knee (448 diffuse, 182 local) were identified as meeting the inclusion criteria, all of which were case series.7,11,14,17,18,20,24-26,30-75 Patients were treated by surgery alone in 19 studies,7,9,11,20,24,26,61-68,70,71,73-75 11 used radiotherapy,17,18,50-57,72 and five used unplanned radiotherapy (with or without surgical synovectomy) as a salvage measure for recurrence or residual disease in a subset of patients.14,25,38,39,60

The 630 patients were followed for a mean of 56 months (17.5 to 112). The mean age across studies ranged from ten to 59 years, with reporting precluding pooling of ages. 45% were women, and 12.2% presented with recurrent PVNS. Open synovectomy was the most common type of treatment (n = 354; 56.2%), followed by arthroscopic synovectomy (n = 239, 37.9%) and combined open and arthroscopic synovectomy (n = 37, 5.9%). Of the 25 studies that used open synovectomy, 13 (52%) used a posterior incision in at least one of their procedures.

**Effect of surgical synovectomy.** The overall rate of recurrence was 21.7% (137/630), 7.1% in the LPVNS group (13/182) and 27.7% in the DPVNS group (124/448) (Table I). Moderate-quality evidence suggests that DPVNS was associated with a 9.06 greater odds of recurrence than LPVNS (95% CI 4.34 to 18.90; p < 0.001). Synovectomy using a combined surgical approach had the lowest reported rates of recurrence (13.5%; 5 of 37), followed by open synovec-
EFFECT OF SURGICAL SYNOVECTOMY AND RADIOThERAPY ON RATE OF RECURRENCE OF PIGMENTED VILLONODULAR SYNOVITIS

Table I. Outcomes by surgical treatment: open, arthroscopic or combined synovectomy

<table>
<thead>
<tr>
<th>No. of knees treated (% of total cases)</th>
<th>Total (43/630)</th>
<th>Open (239/6239)</th>
<th>Arthroscopic (17/630)</th>
<th>Combined (5/37)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>% experiencing recurrence</td>
<td>21.7 (137/630)</td>
<td>20.1 (71/354)</td>
<td>25.9 (62/239)</td>
<td>13.5 (5/37)</td>
<td>O vs A: OR 0.49; 95% CI 0.27 to 0.90, p = 0.021†</td>
</tr>
<tr>
<td>% of DPVNS experiencing recurrence</td>
<td>27.7 (124/448)</td>
<td>24.2 (85/354)</td>
<td>37.8 (54/143)</td>
<td>13.9 (5/36)</td>
<td>CS vs A: OR 0.18; 95% CI 0.06 to 0.53, p = 0.002†</td>
</tr>
<tr>
<td>% of LPVNS experiencing recurrence</td>
<td>7.1 (13/182)</td>
<td>5.9 (6/85)</td>
<td>8.3 (8/96)</td>
<td>0 (0/1)</td>
<td>C vs A: OR 0.19; 95% CI 0.06 to 0.58, p = 0.003†</td>
</tr>
<tr>
<td>% needing reoperation†</td>
<td>6.8 (43/630)</td>
<td>10.5 (37/354)</td>
<td>2.1 (5/239)</td>
<td>2.7 (1/37)</td>
<td>X² = 16.73; df = 2; p &lt; 0.0001‡</td>
</tr>
<tr>
<td>% needing arthroplasty</td>
<td>19.5 (123/630)</td>
<td>16.7 (59/354)</td>
<td>23.8 (57/239)</td>
<td>18.9 (7/37)</td>
<td>X² = 4.69; df = 2; p = 0.096</td>
</tr>
<tr>
<td>% experiencing wound complications</td>
<td>2.7 (17/630)</td>
<td>2.5 (9/354)</td>
<td>2.9 (7/239)</td>
<td>2.7 (1/37)</td>
<td>X² = 0.081; df = 2; p = 0.960</td>
</tr>
</tbody>
</table>

When one localised pigmented villonodular synovitis patient who received combined surgery was excluded from the analysis
† Rates include patients requiring multiple operations
‡ Statistically significant
Odds ratios (OR) of recurrence derived from individual patient meta-analysis. Italicised p-values significant with α level of 0.05; CI, confidence interval; X², chi squared

Tomy (20.1%, 71/354) and arthroscopic synovectomy (25.9%; 62/239).

In multivariable analysis restricted to LPVNS patients, having excluded the only patient who underwent combined synovectomy to allow for convergence of our model, very low-quality evidence found that recurrence was not associated with surgical approach (open vs arthroscopic: odds ratio (OR) = 0.84, 95% CI 0.19 to 3.65; p = 0.81) (Table I). In multivariable analysis restricted to DPVNS patients, low-quality evidence found that recurrence was significantly reduced by either open (OR = 0.47; 95% CI 0.25 to 0.90; p = 0.024) or combined (OR = 0.19, 95% CI 0.06 to 0.58; p = 0.003) synovectomy compared with arthroscopic surgery; however, there was no significant difference between open and combined approaches (OR = 2.49; 95% CI 0.81 to 7.60; p = 0.11).

The incidence of stiffness post-operatively was significantly different between groups (chi squared (X²) = 16.73, df = 2; p < 0.0001), and was present in 10.5% of patients treated with open synovectomy (37 of 354), 2.7% of those treated with a combined synovectomy (one of 37), and 2.1% of those treated by arthroscopic synovectomy (five of 239). Rates of reoperation (for recurrence, stiffness or arthritis), arthroplasty or wound complications were similar in each group (Table I). Only one patient sustained a neurological injury (open synovectomy group; 0.3%; 1 of 354).

**Effect of peri-operative radiotherapy.** As only patients with DPVNS were treated with peri-operative radiotherapy, those with LPVNS were excluded from calculations of the rate of recurrence after radiotherapy but were included in all other subsequent calculations in this section, as limitations in reporting prevented the segregation of data.

Most patients with DPVNS received no radiotherapy (59.8%; 268 of 448), 37.1% received peri-operative radiotherapy (166 of 448), and 14 (3.1%) received delayed radiotherapy as a salvage treatment. External beam radiotherapy was the predominant form of radiation (74%; 123/166 vs. 26%; 43/166 intra-articular radiotherapy). Notably, patients who received either form of peri-operative radiotherapy had the highest proportion of recurrent disease at presentation (81.8% of all initial recurrences; 63/81), extra-articular disease (94.9% of all cases; 37/39), and bone erosions (62.5% of all cases; 10/16).

The overall rates of recurrence were 12.0% (20 of 166) in the DPVNS/peri-operative radiotherapy group and 36.9% (104 of 282) in the DPVNS/no or delayed radiotherapy group. Those who underwent peri-operative radiotherapy and arthroscopic synovectomy had a significantly lower rate of recurrence (10.4%, 5/48) than those who did not receive peri-operative radiotherapy and underwent arthroscopic synovectomy (51.0%, 49/96; X² = 22.99; df = 1; p < 0.001). Those who received peri-operative radiotherapy and open synovectomy had a significantly lower rate of recurrence (12.8%, 13/101) than those who did not receive peri-operative radiotherapy and underwent open synovectomy (31.1%, 52/167; X² = 11.25; df = 1; p = 0.001). Based on small sample sizes, the rates of recurrence in the combined synovectomy group were similar between those who received peri-operative radiotherapy
In multivariate analysis restricted to patients with DPVNS, very low-quality evidence found that the rate of recurrence was reduced with peri-operative radiotherapy (OR = 0.31, 95% CI 0.14 to 0.70; p = 0.006).

Even with LPVNS pooled with the no/delayed radiotherapy group (necessitated by limited reporting in many studies), there was a significant difference that favoured peri-operative radiotherapy in the number of patients undergoing reoperation for stiffness, arthritis and/or recurrence (12.0% or 20/166 vs 21% or 103/474; X^2 test = 8.02; df = 1; p = 0.005). There was no significant difference between groups in terms of overall rates of stiffness, need for knee arthroplasty, or wound complications.

Discussion

Our study is the only systematic review and IPMA of PVNS of the knee, and the largest of the few studies that relate treatment to recurrence. Based on low- to very low-quality evidence from eligible case series, surgical approach does not affect the rate of recurrence in patients with LPVNS, whereas both open and combined open/arthroscopic synovectomy appear to give the lowest rate of recurrence of DPVNS of the knee. The incidence of stiffness post-operatively was highest in those who underwent open synovectomy and lowest in those treated arthroscopically. Other functional results were comparable between the three surgical treatment groups. We found that radiotherapy reduced the rate of recurrence in those treated by arthroscopic or open synovectomy, but not in those treated with combined arthroscopic/open synovectomy.

These results largely echo our hospital's own patient-specific clinical approach. Whereas we manage LPVNS arthroscopically, DPVNS is managed surgically, either by open synovectomy alone or by aggressive arthroscopic synovectomy, including the use of posterior portals, followed closely by open synovectomy to remove posterior or extra-articular disease. We often use adjuvant external-beam radiotherapy in three instances: those with recurrent disease, where surgical synovectomy alone is unlikely to remove all disease (e.g. a large extra-articular extension), or where routine screening identifies residual symptomatic disease post-operatively.

Although surgical techniques have evolved, the overall published rates of recurrence have remained fairly stable. A thorough literature review by Myers et al and Masi,, published in 1980, reported an overall rate of recurrence of 22% among patients with DPVNS who underwent surgical synovectomy, compared with 27.7% in our sample. This may be due to several factors. First, MRI is now the imaging modality of choice to identify the extent of PVNS; it may also identify recurrence earlier or despite the patient being asymptomatic. Secondly, the length of follow-up may have differed. Whereas the mean follow-up in our series was 56 months (17.5 to 112), the length of follow-up in the included studies was not reported by Myers and Masi..

Lastly, there has been a move towards more arthroscopic synovectomy in recent years. In the review by Myers and Masi, 78% of patients underwent open synovectomy compared with 53.7% in our review. As arthroscopy alone was associated with the highest rate of recurrence in our series (37.8%), the increased use of arthroscopic surgery may have resulted in a trade-off between the rate of recurrence and a decreased risk of post-operative stiffness (2.1% vs 10.5% in our series), which has been supported by other studies.

The role of radiotherapy in PVNS is not well defined. A recent survey of 227 German radiotherapy institutions with a 83.2% response rate suggested that only 10% of institutions treated PVNS patients with external beam radiotherapy (47 cases in total), with total doses ranging from 30 Gy to 50 Gy. Local control was achieved in 95.1% of patients, 82.9% having limited or no functional impairment. Of the three studies excluded from our review focusing only on radiosynovectomy, all reported favourable results for both intra- and extra-articular treatment, with good functional outcomes and minimal complications. We found that peri-operative radiotherapy for patients with DPVNS significantly reduced the rate of recurrence. This reduction was most pronounced in the arthroscopic and open synovectomy groups, but had no significant impact on the rate of recurrence after combined synovectomy. Therefore, radiotherapy may have the most impact on patients with residual disease left behind by less aggressive forms of synovectomy. Additionally, although there have been concerns about the adverse effects of radiotherapy on joint function, overall stiffness was comparable between groups (3.6% in those who received radiotherapy vs 8.0% in those who did not). This non-significant decrease in stiffness may be related to a reduced rate of recurrence, and hence a decreased rate of symptomatic intra-articular disease. However, this data is limited by heterogeneous treatment protocols and the pooling of intra-articular and external beam radiotherapy. Although ad hoc subgroup analysis suggests that this occurs when comparing external beam radiotherapy to no radiotherapy (Table II), the small sample size limited similar analysis for intra-articular radiotherapy. We believe these findings are compelling enough to warrant further comparative trials.

Additionally, due to data reporting, DVPNS/LPVNS cases could not be separated out for complication rates in patients receiving no/delayed radiation.

Despite concerns about malignant transformation with PVNS treated by radiotherapy, this review and others have failed to identify any cases of malignant transformation of DVPNS of the knee after radiotherapy in the literature.

Our study has several strengths. We used transparent and systematic methods to search for and select eligible studies. We also ensured the rigorous abstraction of data by using detailed written instructions, conducting duplicate abstraction, and implementing a consensus approach.
Table II. Influence of peri-operative radiation on recurrence rates and outcomes after surgery

<table>
<thead>
<tr>
<th>No. of knees treated (% of total cases)</th>
<th>Total*</th>
<th>External beam radiation</th>
<th>Intra-articular radiation</th>
<th>No/delayed radiation†</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of DVPNS experiencing recurrence</td>
<td>448</td>
<td>123 (275)</td>
<td>43 (9.6)</td>
<td>282 (62.9)</td>
<td></td>
</tr>
<tr>
<td>% of DVPNS experiencing recurrence</td>
<td>22.7</td>
<td>11.4 (14/123)</td>
<td>14.0 (6/43)</td>
<td>36.9 (104/282)</td>
<td></td>
</tr>
<tr>
<td>% experiencing recurrence after open</td>
<td>24.2</td>
<td>10.3 (7/64)</td>
<td>16.2 (6/37)</td>
<td>31.1 (52/167)</td>
<td></td>
</tr>
<tr>
<td>% experiencing recurrence after arthroscopic</td>
<td>37.8</td>
<td>11.6 (5/43)</td>
<td>0 (0/5)</td>
<td>51.0 (49/96)</td>
<td></td>
</tr>
<tr>
<td>% experiencing recurrence after combined</td>
<td>13.9</td>
<td>12.5 (2/16)</td>
<td>0 (0/1)</td>
<td>15.8 (3/19)</td>
<td></td>
</tr>
<tr>
<td>% experiencing stiffness</td>
<td>6.8</td>
<td>3.3 (4/123)</td>
<td>4.7 (2/123)</td>
<td>8.0 (37/464)</td>
<td></td>
</tr>
<tr>
<td>% needing reoperation</td>
<td>19.5</td>
<td>1.0 (13/118)</td>
<td>2.4 (1/464)</td>
<td>0.0 (0/32)</td>
<td></td>
</tr>
<tr>
<td>% needing arthroplasty</td>
<td>2.7</td>
<td>1.7 (2/118)</td>
<td>2.4 (6/253)</td>
<td>0.2 (0/253)</td>
<td></td>
</tr>
<tr>
<td>% experiencing wound complications</td>
<td>0.8</td>
<td>0 (0/118)</td>
<td>0.2 (1/464)</td>
<td>0.5 (1/320)</td>
<td></td>
</tr>
</tbody>
</table>

Grayed out cells within a row were compared statistically and are listed under the significance column

* Based on an analysis with four studies removed for limited reporting
† Rates consider patients requiring multiple operations as only one event
‡ Complications in one study containing five patients treated with external beam radiation, 30 with intra-articular radiation, and five with surgery alone were reported in aggregate and could not be separated; it was therefore decided to exclude these patients from marked analysis as these seven patients requiring reoperation, four requiring arthroplasty and four experiencing wound complications could not be appropriately analysed. As these complications were described in external beam radiation studies alone, no values from intra-articular radiation could be reported. Note: no case of LVPNS was treated with adjuvant radiation. Odds ratios derived from individual patient multivariate analysis. Italicized p-values significant with a level of 0.05
¶ Statistically significant; X^2, chi squared