The management of desmoid tumours at Groote Schuur Hospital: A retrospective review of current practice

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1. Declaration

I, Henrí Du Plessis Pickard, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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2. Dedication

I dedicate this work to my wife, Tricia Pickard, who has supported, helped and encouraged me through so much and without whom this would not have been possible. And also to my three beautiful children, William, Rachael and Benjamin, whom I have been blessed with and give such joy. Lastly, to Jesus, my God and King – from Him, through Him and to Him are all things, to Him be glory forever.

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Background: Desmoid tumours (DT) are rare soft tissue tumours that do not metastasise but are locally aggressive. Management options are varied and the response to treatment can be unpredictable.

Aim: The aim of this study was to describe the clinical presentation, management strategies and outcomes for adult patients who were treated for DT.

Setting: The study was conducted at Groote Schuur Hospital in Cape Town, South Africa, and all patients from 2003 to 2016 who presented with DT were included.

Method: This was a retrospective review of records. Data collected included: demographics, DT-associated conditions, site and size of tumour, histological findings, treatment modalities, follow-up and outcomes.

Results: Seventy patients with histologically confirmed DT were identified. The majority were women (86%) and 77% presented with a painless mass. The commonest site was the anterior abdominal wall (47%). Definitive surgery was performed in 46 (66%) patients, whereas 13 (19%) had definitive radiotherapy. Nine patients received adjuvant radiotherapy post-surgery for involved or close margins. Recurrence developed in 20% of patients post-surgery. In the primary radiotherapy group, one patient had disease progression. Two patients with mesenteric DT died because of bowel obstruction.

Conclusion: This retrospective review of patients affected by DT at a single centre demonstrates the rarity of the condition, the unpredictable natural history and the variety of treatment options available. Many of our findings are similar to other published studies, except the mean size of DT which was bigger. Treatment outcomes following surgery or radiotherapy seem acceptable, although study limitations are noted.

Keywords: desmoid tumour; desmoid fibromatosis; review; management; recurrence; outcome.

Introduction

Desmoid tumours (DT), also known as fibromatosis (aggressive, deep or desmoid-type), are a rare and unusual soft tissue neoplasm. Desmoid tumours result from monoclonal proliferation of myofibroblastic tissue which tends to infiltrate and recur locally, but never metastasise.[1,2] Despite their classification as a benign neoplasm, their capacity for local invasion may cause significant morbidity and even death. Therefore, appropriate and timeous treatment is essential. McFarlane first described the condition in 1832[3] and the term 'desmoids' (from the Greek 'desmos', meaning band- or tendon-like) was coined by Müller in 1838.[4] Desmoid tumours account for 0.03% of all neoplasms and 3% of soft tissue tumours[5,6] and have an estimated incidence of 2.4–4.3 per million people per year in the general adult population.[1] They commonly originate from deep musculo-aponeurotic structures, but also develop intra-abdominally.[2]

Desmoid tumours can occur sporadically (around 85%[7]) or in association with familial adenomatous polyposis (FAP),[1] the latter combination being termed Gardener's syndrome.[8] Pregnancy is an associated condition (either during or following a pregnancy), suggesting high oestrogen states as contributory.[5] The association with antecedent trauma or previous surgery[9] may implicate a dysregulated wound healing process in the pathogenesis of this condition.[8]

Treatment of DT is complicated by the heterogeneity of the condition with regard to natural history, location and symptomatology. Surgery aims to completely excise the tumour with limited functional or cosmetic morbidity, and is generally indicated for symptomatic or progressive DT.[10]

However, recurrence post-surgery is common and is higher in patients with macroscopically positive margins.[7] Radiotherapy (RT) can be used as a definitive treatment modality with results that compare favourably to surgery.[11] Also, when used in combination with surgery, RT appears to decrease local recurrence rates in patients with incomplete surgical excision, particularly following surgery for recurrent tumours.[7] Systemic therapies, including cytotoxic therapies, hormonal therapies, anti-inflammatory agents and biologicals, are also occasionally used.[12] Recently, practice guidelines in many countries have shifted to more expectant management of DT because of increasing evidence that a significant percentage of these tumours may regress or remain stable without any intervention.[10,13,14]

There are limited published data on this condition in low- and middle-income countries. As part of a review of local treatment protocols, the study was conducted to assess the demographics, clinical characteristics, treatment modalities and outcomes of adult patients who were diagnosed with DT, over a 13-year period. This study aims to describe the demographic and clinical characteristics, management strategies, local recurrence and outcomes for all patients treated with DT over this period.

Methods

This was a retrospective review of all patients with histologically confirmed DT who were managed at a single tertiary referral hospital from the 01 January 2003 to 31 December 2016. Patients younger than 18 years of age were excluded and there were no patients identified who had recurrence at initial presentation.

Eligible patient records were identified using established databases from the departments of General Surgery (Surgical Oncology Unit) and Radiation-Oncology. National Health Laboratory Services (NHLS) pathology records were also obtained for all patients diagnosed with this condition during the study period. Data collected included: patient demographics, site and size of DT (combination of clinical, imaging and operative specimen measurement), presenting symptoms, biopsy technique used, associated conditions or risk factors, β-catenin status on immunohistochemistry, primary and other treatment modalities, recurrence rates following surgery, post-operative complications according to Clavien–Dindo classification,[15] mortality events and total duration of follow-up for each patient from the time of diagnosis. Response to definitive RT was assessed according to the response evaluation criteria in solid tumours (RECIST) criteria.[16] Data were stored in a password-protected Microsoft Excel© Spreadsheet.

Statistical considerations

Univariate analyses were conducted given the descriptive nature of the study. Numerical variables were described using measures of central tendency and dispersion, depending on the distribution of the data. Categorical variables were analysed using proportions and two-way frequency tables.

Ethical considerations

Ethical clearance for the study was granted by the Human Research Ethics Committee of the Faculty of Health Sciences at the University of Cape Town (HREC REF: 679/2017).

Results

Patient and tumour characteristics

A total of 70 records of patients who had DT were identified for analysis, as presented in Table 1. The majority of patients (86%) were female. The median age at diagnosis was 36.5 years. The majority of DT, 65/70 (93%), were extra-abdominal, and of these, mainly in the anterior abdominal wall (51%), trunk (29%) and limbs (15%).

The most common presenting symptom was a painless mass, 54/70 (77%). Nine (13%) patients presented with painful mass, three (4%) with bowel obstruction, two (3%) reported

TABLE 1: Demography and clinicopathological findings in patients who had desmoid tumours.

Variables	Value	%	Range
Age			
Median age	-	-	36.5 years
Interquartile range (IQR)	-	-	27.3–45.0 years
Sex			-
Female	60/70	86	-
Male	10/70	14	-
Site			-
Extra-abdominal	65/70	93	-
Abdominal wall	33/65	51	-
Trunk	19/65	29	-
Limbs	10/65	15	-
Head and neck	3/65	5	-
Intra-abdominal	5/70	7	-
Associated conditions			
Familial adenomatous polyposis (FAP)	6/70	9	-
Previous regional surgery	12/70	17	-
Trauma	4/70	6	-
Pregnancy-related desmoid tumours	17/70	24	-
Pregnant – 6-months post-partum	7/17	41	-
> 6-months – 2-years post-partum	10/17	49	-
Presenting symptoms			
Painless mass	54/70	77	-
Painful mass	9/70	13	-
Bowel obstruction	3/70	4	-
Local pain only	2/70	3	-
Unknown	2/70	3	-
Tumour size (N = 58)†	9 cm	-	2 cm – 29 cm
Diagnosis			
Core biopsy	45/70	64	-
Incisional biopsy	13/70	19	
Excisional biopsy	10/70	14	-
Unknown	2/70	3	-
***β*-catenin staining**			
Positive	36/38	95	-
Negative	2/38	5	-

†, Combination of clinical, imaging and operative specimen measurement.

pain localised to the mass and the symptom was not recorded in two (3%) patients. Six (9%) of the cohort were known to have FAP. Of the other factors known to be associated with DT, 7/70 (24%) were pregnancy-related, 12/70 (17%) had previous regional surgery and 4/70 (6%) had a history of previous trauma to the area. Of the 17 patients with pregnancy-related DT, 7/17 (41%) were pregnant or up to 6-months post-partum (one of these patients was noted to have had regional surgery prior to this pregnancy) and the remaining 10/17 (51%) were diagnosed between 6 and 24 months after delivery. Thirty-one patients (44%) had no known associated condition.

The diagnosis was based on histological samples obtained by core-needle biopsy in the majority of cases 45/70 (64%), whereas excisional biopsy was relied on in 13/70 (19%) and incisional biopsy in 10/70 (14%). The original diagnostic investigation was not specified in 2/70 (3%) of the records. Immunohistochemistry staining for β-catenin was performed in 38/70 (54%) cases and 36/38 (95%) of these were positive. Of the 6 patients with confirmed FAP, only one was tested for β-catenin and was poistive. Tumour size was known in 58/70 (83%) patients and ranged from 2.0 cm to 29.0 cm at greatest dimension, with an average size of 9.0 cm.

Treatments and outcomes

The majority of patients, 58/70 (83%), were managed by the Endocrine and Oncology Surgery Unit within the Division of General Surgery and by the Radiation Oncology Department, the remainder having been managed by the Gynaecological and Orthopaedic services. Thirty-six (51%) patients were formally reviewed within a multidisciplinary team (MDT) context, which varied in terms of relation to primary treatment intervention, with many having had primary surgery prior to MDT. The definitive treatment modalities are depicted in Figure 1.

Surgery

Surgery was the primary treatment in 46/70 (66%) patients; 44/70 of these were surgery performed with curative intent and 2/70 were palliative debulking procedures. Of the 44 patients who underwent surgery with curative intent, 28/44 (64%) had clear (R0) margins, 11/44 (25%) had microscopic (R1) involved margins and 2/44 (4%) had macroscopic (R2) involved margins; in the remaining 3 (7%), the final histology report was not available. Twenty-six patients had wide local excisions of abdominal wall DT and of these 23 required mesh reconstruction of the abdominal wall defect. The surgical complications are shown in Table 2.

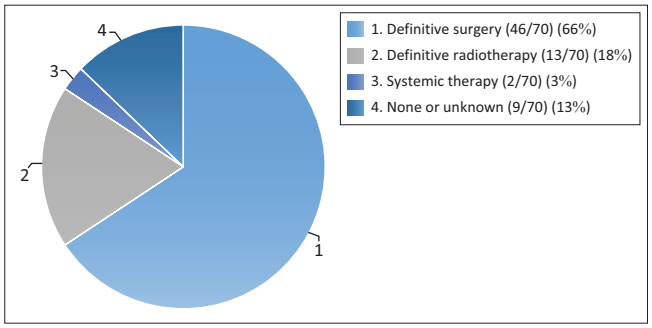

FIGURE 1: Breakdown of definitive treatment modality used.

Surgery and radiotherapy

Combination treatment with surgery and RT was used in 11 cases. Nine received adjuvant RT and 2/11 neo-adjuvant RT. In the adjuvant category, 8/9 cases had involved margins (7 = R1, 1 = R2) and one case had a close margin (2 mm). In the neo-adjuvant category (to downsize the tumour prior to surgery), one had macroscopically involved (R2) margins at surgery and progressed (this patient had the debulking surgery for tumour necrosis), and the other had clear (R0) margins at surgery.

Radiotherapy as definitive treatment

Definitive RT was employed in 13 patients in whom the DTs were deemed irresectable. Of the patients who received RT as definitive treatment, nine (69%) had a partial response, one (8%) had a complete response, two (15%) had stable disease and one (8%) had progressive disease as assessed using the RECIST criteria.[11] See Figure 2.

These patients were all followed up for more than 1-year post-RT, with an average follow-up of 57 months (range: 13–133 months). Radiation complications included six cases of skin fibrosis. The median RT dose delivered (including definitive, adjuvant and neo-adjuvant) was 55.0 *Gy* (range: 46.8 *Gy*–62 *Gy*) given in 2 *Gy* fractions.

TABLE 2: Surgical complications (early or late) Clavien–Dindo classification system.[15]

Grade	Complications	Management	No. of patients
Grade 1	Seroma	Conservative	6
	Chronic pain syndromes	Analgesia	2
	Surgical site infection	Standard wound care	1
	Incisional hernia	Conservative	1
Grade 2	Surgical site infections	Oral antibiotics (in addition to standard wound care)	2
Grade 3a	Seroma	Percutaneous drain placement	1
Grade 3b	Incisional hernia	Repair with mesh	4
	Enterocutaneous fistula	Surgical resection	1
Grade 4a	-	-	-
Grade 4b	-	-	-
Grade 5	Bowel obstruction	-	2

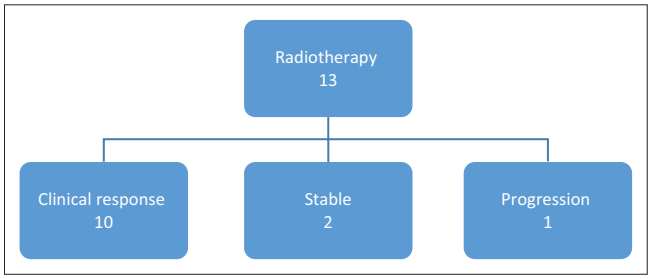

FIGURE 2: Response to definitive radiotherapy treatment.

Systemic treatments

Of the six patients who received systemic therapy, four had this in combination with RT. Only two patients had systemic therapy as their only treatment modality with one receiving imatinib with a good response and one received tamoxifen and non-steroidal anti-inflammatory drugs (NSAIDs) with no demonstrable response. Two patients received chemotherapy (six cycles of doxorubicin), and two tamoxifen, as an adjunct to definitive RT. Active observation alone was not formally used as a primary management strategy in any of our patients.

Follow-up

Forty-two patients had adequate follow-up of more than 1 year and 15 had follow-up for less than 1 year. The median follow-up for this combined group of patients was 29 months, with one patient having been followed up for 295 months (almost 25 years). For the remaining 13 patients, follow-up length could not be determined because of missing clinical notes.

Recurrence post-surgery

Local recurrence after surgery (surgery alone or surgery with RT) was only analysed in those patients who followed up for a year or more. This consisted of clinical examinations and radiological imaging. The outcomes are summarised in Figure 3. The total number of patients in this category was 25/44 (57%) who had surgery, with 19/44 (43%) patients considered as 'unknown' in terms of recurrence because of inadequate follow-up. None of the patients with inadequate follow-up was noted to have evidence of recurrence at last follow-up. Of the 25 patients with adequate follow-up, 5/25 (20%) had proven recurrence, and 20/25 (80%) had no evidence of recurrence. All patients with recurrence had either microscopically (three patients) or macroscopically (two patients) involved margins. Of the patients with no recurrence, 15/20 (75%) had clear (R0) resection margins and 5/20 (25%) had microscopically involved (R1) resection margins, as depicted in Figure 4. The average age at presentation of patients who had recurrence post-surgery was 25 years (range: 18–32).

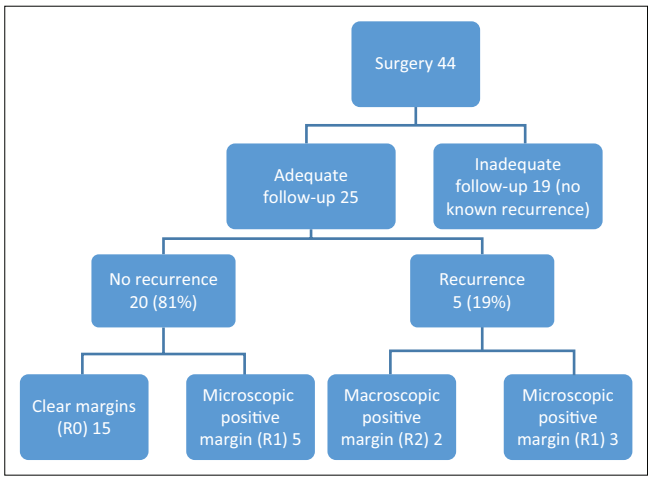

FIGURE 3: Outcome of surgical management.

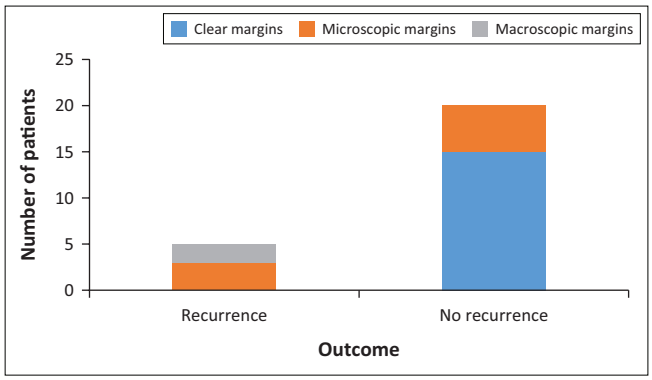

FIGURE 4: Surgical margins and recurrence.

Mortality

Four patients in our cohort are known to have died, two of unrelated medical causes, while the other two were as a result of the DT. Both of the patients who had died of DT had intra-abdominal disease with bowel obstruction because of disease progression.

Discussion

The demographic profile of study patients with DT is similar to other published studies with the majority being female with a median age in the fourth decade and the majority being sporadic DT.[17,18,19,20] Sporadic DT affects β-catenin production with the mutation being in the CTNNB1 gene, whereas in FAP-related DT, the mutation is in the adenomatous polyposis coli (APC) gene.[12] Positive *β*-catenin immunohistochemistry in those tested (38/70 – 54%) in this study was much higher (95%) than the reported rate (67% – 80%) in other studies.[21] Unfortunately those with FAP were not all tested for β-catenin status, but the one tested was did express β-catenin as one would expect. The average size of desmoids in the current study was 9.0 cm (range: 2.0 cm – 29.0 cm), which is larger than other similar reports, where the mean was between 6.3 cm and 7.7 cm.[2,20] Larger size at presentation is significant as size greater than 7 cm has been shown to be a poor prognostic factor for progression-free survival.[13]

In terms of the location, the majority (93%) of patients had extra-abdominal DT which is similar to a report from a study involving 426 patients by Salas et al.,[13] which showed 87% of DT to be extra-abdominal. Interestingly, only one of the six confirmed FAP-associated DT cases was intra-abdominal (four were located in the abdominal wall and one in the neck region). This preceding finding is unusual as the majority of reported DT associated with FAP are intra-abdominal, followed by the anterior abdominal wall. Pregnancy (previous or current) was noted in close to 25% patients. Similar to what is reported in the literature,[22] over two-thirds of pregnancy-related DTs occurred in the anterior abdominal wall and this group had a good outcome with a local recurrence below 5%.

The majority of patients underwent surgery as their primary treatment with the aim of achieving clear surgical margins. The rates of R0 and R1 surgical resections rate in our cohort are comparable to published studies despite relatively late presentation and large tumour size. However, the clinical

relevance of achieving clear surgical margins and its impact on local recurrence is not clearly proven and is the subject of conflicting reports in the literature.[7] In a series by Gronchi et al.[23], there was no significant difference in disease-free survival in those with microscopically negative or positive surgical margins, although there was a trend towards significance in patients with microscopically positive margins after repeat surgery for local recurrence. In a systematic review in 2017 which included 16 studies and 1295 patients,[7] microscopic margins did seem to be an important factor with an almost twofold increase in risk of recurrence for patients treated with surgery alone and positive microscopic margin. In our series, there was no local recurrence detected in those with negative surgical margins; however, the sample was too small to prove statistical significance. There were three local recurrences in patients with microscopically positive margins and two local recurrences in patients with macroscopically positive margins.

Another subject of contention in the management of DT is the role of adjuvant RT following surgery with involved margins, with some series showing a local control benefit[11,24,25,26] and others showing no clear benefit.[23,27] In our series, the effect of adjuvant RT cannot be determined because of the small sample size, heterogeneous treatment regimens and lack of adequate follow-up.

Factors associated with recurrence noted in published literature include age < 37 years, tumour size > 7 cm in diameter and extra-abdominal location.[13] The average age of patients with recurrence in our series was 25 years compared to the overall mean age of 37 years. Neo-adjuvant RT has been used with promising results in some centres,[28] but in our series, only two patients received neoadjuvant RT with one proceeding to an R0 resection with no recurrence and the other with no response to RT.

Radiotherapy as definitive treatment is an acceptable alternative treatment to surgery, with local control rates as high as 90.9% at 3 years, including 13.6% complete responses, 36.4% partial responses and 40.9% stable cases being reported.[29] Our results showed local control rates well over 90% in patients treated primarily with RT, with over 77% of cases attaining either complete or partial response. The average follow-up was close to 5 years, and it is important to note that the effects of RT can be slow and ongoing even beyond 3 years.[29] This response was measured according to the RECIST criteria despite its limitations in assessing the slow response of some tumours to RT.[16]

Systemic therapy, previously employed only in situations where surgery was not an option (e.g. intra-abdominal FAP-associated DT), is becoming a more commonly used option in the management of DT.[12] It consists of non-cytotoxic therapy and cytotoxic therapy. The non-cytotoxic therapies include hormonal agents (e.g. tamoxifen), anti-inflammatory agents (NSAIDS) or biologicals (imatinib, sorafenib).[12,30] The cytotoxic therapies include chemotherapy agents such as doxorubicin, vinblastine and methotrexate.[1] Other newer local treatments include local ablative therapies using thermal or chemical means (e.g. isolated limb perfusion with tumour necrosis factor alpha),[31] particularly in those poorly suited to surgery.[10] The use of systemic therapy in our setting was limited to only a few patients and in heterogeneous treatment settings. Only doxorubicin had a clinically significant impact with a good response in one of the patients managed with this agent.

Active surveillance for 1–2 years for DT is a management strategy that has been adopted by many guidelines in recent years.[7,10,14,32,33] This strategy has developed because of reports that up to 15% of DT regress spontaneously and a significant number remain stable with a progression-free survival of up to 50% at 5 years.[34,35,36] These findings have brought into question traditional therapies, primarily surgery, as the mainstay of treatment, particularly in cases where surgical excision results in significant morbidity.[13] The aim of active surveillance is to determine which DTs are aggressive and will progress and which are indolent, slow-growing or may regress. Unfortunately, to date, there are no reliable biological markers to distinguish these two groups although genetic mutations in the CTNNB1 gene are being investigated.[37] Because of the time frame of our study, none of the patients in our study underwent an active surveillance strategy, although it is clearly a preferable option to reduce patient morbidity and also to limit unnecessary procedures in our resource-limited setting. When considering the safe implementation of this strategy in our local context, the issues of late clinical presentation, delay in referral pathways, larger tumour size and poor follow-up will need to be taken into consideration.

Limitations

This study has many obvious weaknesses, including being retrospective, small sample size, poor follow-up, heterogeneous treatment regimens and missing or incomplete patient records. This impacts the external validity of the study findings. Associations between clinical characteristics and outcomes could not be explored further because of the small sample size.

Conclusion

This retrospective review of patients affected by DT demonstrates the rarity of the condition, the unpredictable natural history and the variety of treatment options available. While many of our findings mirror previously published studies, the mean size of DT in this series was greater, possibly because of later presentation or delayed referral. The majority of patients in this series underwent surgical management and a subset of patients were treated with adjuvant or definitive RT. Systemic treatments played a minor role. While surgical and RT treatment outcomes in this series were acceptable, strong conclusions cannot be drawn because of small numbers and inadequate follow-up. Newer treatment approaches emphasising active surveillance may need to be incorporated into our management protocols but

with an awareness of the specific clinical context and through an individualised multidisciplinary decision-making process.

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Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contributions

Research topic and initial planning were done by E.P. Data collection, analysis and manuscript composition were performed by H.P., with guidance from L.C., E.P., N.J. and T.N. Senior review, expert consultation and final documentation approval were performed by L.C., E.P., N.J., F.M. and T.N.

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Data availability statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Disclaimer

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5. Appendices

a. Human Research Ethics Approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6626
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

09 October 2017

HREC REF: 679/2017

Prof E Panieri
General Surgery
J-Floor, OMB

Dear Prof Panieri

PROJECT TITLE: THE MANAGEMENT OF DESMOID TUMOURS AT GROOTE SCHUUR HOSPITAL: A RETROSPECTIVE REVIEW OF CURRENT PRACTICE (MMED CANDIDATE - DR H PICKARD)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 October 2018.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

The HREC acknowledge that the student, Dr Henri Pickard will also be involved in this study.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical

Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI),and Declaration of Helsinki (2013) guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

b. Groote Schuur Hospital Approval

Western Cape Government
Health

GROOTE SCHUUR HOSPITAL
Enquiries: Dr Bernadette Eick
E-mail : Bernadette.Eick@westerncape.gov.za

Professor E. Panieri
General Surgery

E-mail: Eugenio.Panieri@uct.ac.za / henripickard@gmail.com

Dear Professor Panieri

RESEARCH PROJECT: The Management Of Desmoid Tumours At Groote Schuur Hospital: A Retrospective Review of Current Practice (MMed Candidate Dr H. Pickard)

Your recent letter to the hospital refers.

You are granted permission to proceed with your research, which is valid until **30 October 2018.**

Please note the following:

a) Your research may not interfere with normal patient care.
b) Hospital staff may not be asked to assist with the research.
c) No additional costs to the hospital should be incurred i.e. Lab, consumables or stationary.
d) **No patient folders may be removed from the premises or be inaccessible.**
e) Please provide the research assistant/field worker with a copy of this letter as verification of approval.
f) Confidentiality must be maintained at all times.
g) Should you at any time require photographs of your subjects, please obtain the necessary indemnity forms from our Public Relations Office (E45 OMB or ext. 2187/2188).
h) Should you require additional research time beyond the stipulated expiry date, please apply for an extension.
i) Please discuss the study with the HOD before commencing.
j) Please introduce yourself to the person in charge of an area before commencing.
k) On completion of your research, please forward any recommendations/findings that can be beneficial to use to take further action that may inform redevelopment of future policy / review guidelines.
l) Kindly submit a copy of the publication or report to this office on completion of the research.

I would like to wish you every success with the project.

Yours sincerely

DR BERNADETTE EICK
CHIEF OPERATIONAL OFFICER
Date: 25 October 2017

C.C. Mr L. Naidoo
Dr B. Jacobs
Professor E. Muller

G46 Management Suite, Old Main Building,
Observatory 7925
Tel: +27 21 404 6288 fax: +27 21 404 6125

Private Bag X,
Observatory, 7935
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c. South African Journal of Oncology Review Process

Ref. No.: 68
Manuscript title: The Management of Desmoid Tumours at Groote Schuur Hospital: A Retrospective Review of Current Practice
Journal: South African Journal of Oncology
****

Dear Dr Henri Du Plessis Pickard

We thank you for the submission of your manuscript. The peer review process of your manuscript has now been completed and we have reached a decision regarding your submission.

At present, your manuscript requires minor revisions to address the comments of the reviewers. Their comments are attached to the email and/or to the bottom of this letter. If not, for your convenience log onto your profile to view the reviewers' comments.

Please include with your revised submission an itemised, point-by-point response to the reviewers which details the changes made. The revised manuscript should be submitted by 25 January 2019; if you anticipate that you will be unable to meet this deadline, please notify the Editorial Office.

Below my signature, you will find steps to resubmit your revised manuscript. If you need any assistance, kindly contact the Editorial Office at submissions@sajo.org.za with any questions or concerns.

We look forward to receiving the revised manuscript.

Yours sincerely,
Prof. Raymond P. Abratt
Department of Radiation Oncology, University of Cape Town; and, Department of Clinical Governance, Independent Clinical Oncology Network
Phone 0731729507
Raymond.Abratt@uct.ac.za

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Frequently Asked Question
How do I view the reviewer comments, after the formal peer review, if the Editor-in-Chief provided feedback regarding my article?
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The editor should send you an email stating all the revisions suggested during the formal peer review process. If you are advised to download the comments via your personalised journal section, follow these steps:

- Log into your personalised journal section in the journal.
- Under your ‘User Home’ click on the ‘Author’ or ‘Active’ link that will direct you to your ‘Active Submissions Table’.
- Under the ‘Status Column’, click on ‘In Review: Revisions Required’. This link takes you to the overview of the peer review process.
- The review page of your article provides information and documentation under the heading ‘Peer Review', and will identify files by reviewers, e.g. Reviewer B 19-123-1-RV.docx 2011-08-10. Download these documents to view the reviewer files.

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Frequently Asked Question: The Editor-in-Chief has requested revisions to my article. How do I submit my revised version?

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When the editor dealing with your submission chooses to ask for a revision, you will be notified by email. In the journal’s personalised section your submission will move in the active table from the status ‘In Review’ to ‘In Review: Revisions Required’.

When you prepare a revised version of your manuscript, it is essential that you carefully follow the instructions given in the editor’s letter. Use the standard uploading format (as described for original submissions), but include both a clean copy of your manuscript and an annotated copy describing the changes you have made. Failure to do so will cause a delay in the review of your revision.

If references, tables, or figures are moved, added, or deleted during the revision process, renumber them to reflect such changes so that all tables, references (Vancouver Style) and figures are cited in numeric order. Images need only be uploaded if changes have been made to the figures since the previous version.

The annotated copy should have highlights on the changes (either by using the 'Track Changes’ function in Word or by highlighting or underlining text) with comments in the text referring to the editor or reviewer query. Be sure when you upload your annotated version that the changes are clearly visible on the Word (.doc) file prior to resubmission.

You should create a point-by-point response letter specifying how you have addressed each of the editor’s and reviewer’s comments.

Using the review version of your manuscript, edit and revise your submission according to the reviewers' and editor's comments, and follow the steps:

- When you have addressed the comments and completed your revisions, log into your journals’ personalised section and click on ‘In Review:

Revisions Required'.
- Under the 'Editor Decision', click on the bubble icon to view the editor's decision letter. If needed, you may view the original editor and reviewer comments by clicking files linked under the 'Review Round'.
- Once your revisions are correctly formatted and prepared, click on 'Browse' to begin uploading your revised manuscript from your desktop. Ensure to upload a clean, annotated and point-by-point version as part of your revised manuscript submission.

Once all three documents are uploaded, you will need to inform the editor via email of your resubmission. Click on the email icon and proceed to type and email the editor. Remember to press 'Send'.

i. Reviewer A comments

Please find my comments and corrections in line. This is important and relevant research that should be published and fits the target audience of SAJO. There are however a number of issues that need to be reviewed and addressed before it can be deemed fit for publication. The major issues concern the unmet secondary aim and its analysis, the reporting format of the outcomes and the final conclusion.

Abstract

- I do not see where the secondary aim is reported on in the results section. Please clarify. If this secondary aim was not met in terms of validity and robustness of the statistical analysis, I would strongly suggest leaving it out. I have left this out as my focus in this study is for it to be a descriptive study and the small numbers and incomplete data don't make it easy to meet the secondary aim
- Suggest "associated conditions" as in main methods section. Done
- Please specify if these are mortality and recurrence statistics, rates or ratios? Statistics – I have changed the wording to make this clearer
- See later comments on the use of the terms primary vs definitive. Noted
- Due to the small numbers and inconsistent follow-up it would be incorrect to compare the current outcome results with other series. The conclusion has been changed
- Please explain if this management strategy is being put forward as applicable to all DT as could be inferred from this sentence or a specific subset. The conclusion has been changed

Introduction

- Comment: "condition" is too vague a term to use here when considering the non-oncological readership of SAJO. Suggest specifying "soft tissue neoplasm." Done
- The inability of desmoids to metastasize or dedifferentiate is a distinctive feature and I would strongly suggest moving the last sentence of this paragraph to this position before making reference to its association with morbidity and mortality. Done

- There is a vast difference in the epidemiology of soft tissue tumour subtypes between adults and children. Please explain why it is not relevant to specify the age group that this incidence rate refers to or at least the age group most affected by DT. Added “adults” to clarify this
- Review sentence construction. “Other associated conditions…” suggests more than one condition being listed in one sentence i.e. pregnancy and antecedent trauma. Noted and changed
- The abbreviation DT was defined in the plural form in the first line. Review for consistency of abbreviation use. Good point – changed to be consistent throughout article
- Review reference. The reference to a general medical database is not ideal and also outdated (accessed 2 years ago). I would suggest referring to specific studies ie. ref 7&18, clinical guidelines or update the reference. There was an issue with my references following editing and somehow even though I had used a reference manager, some of the superscripts lost their link to a reference and became merely numbers?! I have gone back and reconnected the numbers to the appropriate references
- Please provide a reference for this statement. This statement could be interpreted to imply that RT offers a LR benefit for all DT and this would be incorrect. Ref 7 states that “adjuvant RT has not demonstrated a conclusive benefit after first surgery regardless of resection margins. However, adjuvant radiotherapy may reduce the risk of recurrence after incomplete surgical resection, particularly in patients with recurrent tumours. [7] Have changed the statement
- Suggest clarifying this statement by adding “without any intervention.” Done
- Consider referring to low- and middle-income countries as this is an accepted classification system used by the WHO when comparing world-wide disease patterns. Done

Methods

- Please specify if patients with recurrent DT at first presentation to your centre were excluded. I have specified
- Consider specifying in the introduction that this report concerns adult STS. Done
- All the diagnoses were based on histology as this was an inclusion criterium for the study. Suggest changing this to “biopsy technique used”. Done
- Consider changing to “immunohistochemistry”. Done
- Please explain why recurrence rates/ ratios are not mentioned here as it is part of the primary aim of the study under “Aim” and reported in detail in “Results”. I have corrected this omission
- Please specify from which time-point follow-up was calculated. Done

Statistical Considerations

- Bivariate data reporting in terms of reporting the margin status of the patients who recurred or did not recur as in the “Recurrence” section is valid. This does however not constitute bivariate analysis as the low numbers do not allow for this. I have changed this and removed Bivariate analysis, which was attempted but not included.

Results

- Avoid duplication of detailed results, i.e. statistics and full breakdown, in both the text of the results section and in tables. I strongly suggest only highlighting selected results in the text. I will attempt to take out some
- Suggest adding subheadings i.e. Patient and tumour characteristics, Treatment, Follow-up and Outcomes. Good Idea – I have done so
- Suggest replacing with: The majority of patients (86%) were female. Done
- In a tumour that typically targets a defines age group i.e. the fourth decade, it would be more relevant to report the median age of the cohort. This would also be more comparable to the same statistic in other series as is done in the discussion. Have changed to "median"
- Consider grouping limb lesions together as is the trend in most reported series on DT. Done
- Important to specify whether the pain was related to the mass and not arising from somewhere else. Suggest: "painful mass". Done
- Important to indicate in some way that the pain was related to the DT. Suggest: "localised pain". Done
- Please specify if this refers to the time of formal diagnosis or when the patient became aware of the lesion? Have specified
- It would be relevant to indicate if any patient had more than one associated factor i.e. pregnancy and surgery, as it has been reported that pregnancy related surgery can be associated with DT. Found one patient that did
- Indicate percentage of cohort tested for β-catenin (54.3%) as well as percentage staining positive out of the whole cohort (51.4%). It would be a misrepresentation to report the rate of stain positivity as 95% (In discussion) if just more than half of the cohort were tested. I have modified this to give a more honest representation
- Suggest summarizing as "Only 17% of cases were not primarily managed by the ……" I did try this but it ended up me saying the same thing but in reverse and seemed a bit more clumsy – so have left it. I'm happy to change it but not quite sure how.
- In view of the recommendation made in the conclusion, it would be relevant to specify in how many cases this review occurred before the first definitive treatment intervention i.e. surgery or RT. Unfortunately I do not know the answer
- Using the terms "primary" and "definitive" interchangeably in the following 3 sections could lead to confusion. Does primary refer to the first/ up-front intervention or the definitive/ most important intervention? Suggest using either one of these terms consistently or clarifying the difference between the 2 in the text. Have used only one term to make it clearer and more consistent.
- According to this pie chart 59 patients had surgery or RT or both. That would mean that the 2 neo-adjuvant RT patients mentioned under "Surgery and Radiotherapy" are included in the 46 under primary surgery and that the 13 Primary radiotherapy cases represent the 13 cases discussed under "Radiotherapy as definitive treatment". It would then be relevant to mention that 2 of the 46 patients had neo-adjuvant RT as reported in "Surgery and Radiotherapy". One would then deduce that these 2 patients represent one of the 2 R2 cases mentioned here and the other forms part of the R0 cohort mentioned here. Please confirm if this is correct. It also makes the special mentioning of the patient who had "palliative surgery" for tumour necrosis confusing. Was this patient also included in the 11 patients who had surgery and radiotherapy? The deductions in this comment are correct. The patient who

underwent a palliative resection does fall into the category of surgery. Detail of the two palliative surgery cases was removed in order to improve clarity.

Surgery

- Please explain the specific reference and setting apart of these 2 patients. One could argue that the debulking procedure for bowel obstruction was in fact a planned R2 resection and that the second case with tumour necrosis should be grouped under the definitive RT cohort with special mention that the patient ended up requiring salvage surgery. At the same time it could also refer to a case of neo-adjuvant RT followed by planned surgery. See other comments related to this second patient as well. I have removed some of the detail of some of these patients and tried to make it clearer
- Technically the RT and not the surgery was the primary treatment in this case unless it was neo-adjuvant RT followed by planned surgery. See other comments on this patient. This is one of the "neo-adjuvant" cases
- This abbreviation is unnecessary as this term is not used again in the article. Well picked up
- Consider changing to "required". Done
- Suggest referring to this table in the text to place it into context. Done
- Suggest reformatting this column as a list with complication first and number of cases second. Suggest reformatting by adding column right with "management". Suggest deleting. CD Grade 5 implies death already. Complication table adjusted

Surgery and RT

- Please specify if this includes the patient who had surgery for tumour necrosis mentioned under "Surgery". Specified
- Neo-adjuvant RT is not a well described treatment modality in DT as it is for other adult STS. Please explain the rationale and supporting data for this management strategy further and if it was in fact planned neo-adjuvant RT or definitive RT with salvage surgery due to progression. This was planned neoadjuvant radiotherapy which was an individualised MDT decision based on the difficult surgical options for the patient's concerned.
- It would be relevant to specify if these margins were R1 or R2 as R2 is a known risk factor for increase local recurrence. Have specified
- This sentence and the last part of the final sentence is somewhat out of place here as recurrence is discussed under a later heading. See comment on "Recurrence" heading. Have adjusted this
- Please specify if this was "adequate follow-up" as defined later. Yes – all for more than a year

RT

- Please specify if this cohort includes the patient who had surgery for tumour necrosis mentioned under "Surgery". No – this patient is in the "surgery" group
- The reference to non-definitive RT in this sentence can be confusing. Suggest moving this sentence to the end of the paragraph. Have done so

- It would be more relevant to report the median and dose range used as RT dose prescriptions are pre-defined according to protocol and can therefore be seen as categorical rather then continuous. Done
- Please specify if this was the dose ultimately delivered or the planned/ prescribed dose. Delivered
- Using the terms "primary" and "definitive" interchangeably could lead to confusion. Suggest using definitive consistently. Will use "definitive"
- These 3 sentences are somewhat out of place here as Systemic treatment, follow-up and recurrence are discussed under later headings. See comment on "Recurrence" heading. This is a good point I have changed it to "treatment and outcomes" as putting all the outcomes together doesn't seem to work as it is quite different comparing outcome post surgery and post RT

Recurrence

- There are multiple issues with the reporting of outcomes in this article: 1. This section only reports the recurrence after primary surgery. This would make the heading somewhat misleading. The recurrence after definitive RT is reported in the "Radiotherapy as definitive treatment" section. Please group all reporting of outcomes under one heading to avoid confusion. I have included outcomes with treatment – to make it easier to understand 2. Suggest moving this section to after the "Follow-up" section as the quality of outcome data depends on the quality of follow-up which in this cohort was one of its weaknesses. Done 3. The decision to report outcomes by dividing the cohort into those patients with more or less than one-year follow-up is somewhat confusing and dilutes the significance of the results. Ref 7 reports that most recurrences occur within 2 years of surgery. Please explain why this strategy was chosen. Why one year was used as follow up? This was a time length decision as most patient who had follow up attended clinic appointments for the first year. We acknowledge that this is an inadequate timeframe hence strong conclusions cannot be drawn about local recurrence and outcomes. 4. The reporting of deaths is grouped under "follow-up" whereas it would fit better with the other outcomes under one heading. Will do so
- Specify whether this was based on clinical examination alone or on radiological findings. Done
- Specify "at last follow-up." Done
- These are the results that could be used for bivariate analysis (see comment on Secondary aim and statistical analysis) to test for correlation or association. Unfortunately, the low numbers do not allow for this. It could be visually represented in a stacked bar or column chart. As previously mentioned – decided to remove "secondary outcome"
- Please explain the relevance of reporting of the age at time of recurrence. Ref 18 indicates that age at diagnosis ≤37yrs is associated with worse PFS outcomes, this would be a more relevant finding to report. It would also be relevant to report RFS (in months post-op) if possible. This is a mistake – it was age at diagnosis, and this has been corrected
- Suggest referring to this figure in the text to place it into context. Suggest adding foot-note specifying adequate follow-up as ≥1 year follow-up. Suggest placing "No

recurrence" arm on the left and "Recurrence" arm on the right of the flow diagram. All done

- It would be relevant to have a similar flow chart for definitive RT patients or to expand the current chart to include them. I have done so

Systemic Treatment

- Please specify where the 3 patients referred to under "Radiotherapy as definitive treatment" (Systemic therapy was given to the 3 patients who had no response to RT) fit into this section. Please explain how these 4 patients relate to the 2 patients who received primary systemic therapy in the pie chart in Figure 1. Please specify timing of this treatment i.e. pre-surgery or after local recurrence? I have changed this section in an attempt to clarify "systemic therapy" comments
- The decision to divide the cohort into those patients with more or less than one-year follow-up is somewhat confusing and dilutes the significance of the results. I suggest reporting median follow-up length from first treatment intervention for all patients with any known follow-up visit. Please explain why Kaplan Meyer curves cannot be used to estimate a local recurrence rate at certain relevant time intervals i.e. 5yrs, 12m or 6m (with censoring of the patients at last follow-up). Given the incomplete data and small sample size, time to event data were not analysed further.

Follow-up

- Please specify if follow-up was according to a strict schedule and if it entailed clinical examination only or radiological investigations. It was extremely variable – no strict schedule
- It would be more relevant to report the median follow-up duration if one case is an outlier. Done
- These two sentences report outcomes and should be grouped with the reports on recurrence under one heading preferably following this one. Have made a "mortality" subheading
- Suggest specifying if this was due to progressive DT or complications of its treatment. Done

Discussion

- This is an incorrect deduction as 46% of the cases were not tested for β-catenin at all. At most one can claim that at least 51% of the patients were BC positive. Noted and tried to explain this more accurately
- Please explain why it would not be relevant to mention the relatively high rates of R0 and R1 resections achieved in this cohort for upfront surgery despite large presenting tumours and likely surgical service constraints. The results look good (from my calculations) and quite comparable to those in Ref 7. Have done so
- Suggest adding "for local recurrence". Done
- Please confirm if this sentence refers to the bivariate analysis mentioned in the secondary aims. If this is what it refers to, I would suggest stating that the small sample size, heterogenous treatment regimens and lack of follow-up precluded analyses of any associations between descriptive factors and outcomes. Have edited

- Please explain the relevance of this sentence. It might be more relevant to report on the number of recurrences in the patients with positive margins and adequate follow-up who had surgery only here. Removed sentence
- Suggest changing to "cannot be determined due to the small sample size, heterogenous treatment regimens and lack of follow-up. Done
- Please explain the relevance of this statement. Would it not be more relevant to discuss the number of recurrences in patients with positive surgical margins and adequate follow-up that did and did not have RT? Removed
- Please clarify if this age (25yrs) refers to the age at diagnosis or at time of recurrence as mentioned earlier "The average age at time of recurrence was 25 years (range: 18 – 32)". Please note that the prognostic data in Ref 18 refers to age at diagnosis and that 13% of the patients in that cohort were <18yrs of age. Age of diagnosis – corrected
- Please provide specific reference within ref 28 for this statement. This is true for STS in general, but not for DT. Correct reference added
- It is also relevant to note that these cases were all deemed irresectable and therefore were probably in a poorer prognostic group than the patients who had upfront surgery. Please comment on this. Section edited – have not specifically commented on this
- Please explain the reference to resectable DT here. It is my understanding that AS is promoted for asymptomatic or minimally symptomatic DT whether resectable or not as an initial treatment option to monitor for possible spontaneous regression or stability. Definitive intervention would then be triggered by progression or progressive symptoms. Have taken out "resectable"
- It is interesting to consider the referral pathways of your setting and whether tumours that are referred to a tertiary referral centre might not already have been observed clinically for a long period of time in the primary or secondary care setting and only get referred when they don't regress spontaneously or become symptomatic. This represents a form of referral bias. It is interesting
- Consider summarizing the inherent study weaknesses under one heading or paragraph. Have done so

Conclusion

- Please provide a reference for this caveat. Caveat was removed

ii. Reviewer C comments

Thank for the opportunity to review the manuscript. It is definitely of importance and relevance across various medical specialties. For comprehensive inputs and suggestions please see attached manuscript with Track Changes.

1. Title: Ok.

2. Abstract

a)Aim: Ok

b) Methods: Ok

c) Results: Check denominators and be consistent with style of reporting.

d) Results: Need to be re-done to be based on findings from the study. Has been changed

e) General: Check grammar.

3. Introduction

a) Otherwise Ok.

b) Ensure that references follow each other sequentially. Check appearance of References 11-15. Problem with references sorted out – technical issue

c) Consider including information on morbidity associated with resection of DT and therefore citation of an article covering the Clavien-Dindo Classification within the introduction. Have done so

d) General: Improve grammar.

4. Methods

a) Reasonably ok.

b) Add post-operative complications amongst data to be collected. Done

c) Provide more details regarding statistics to be used. Edited section

5. Results

a) Be consistent regarding reporting: Numerator/Denominator (%). Done

b) Use tables and figures strategically and not repeat everything which is contained in them in the text. Okay

c) Caption for tables on top and for figures below. Done

d) Captions should be comprehensive i.e. should be able to tell the story. Have edited as suggested

e) Tables and figures should appear immediately after they have been cited/referred to. Good point

f) Revise grammar.

g) Appropriate use of numbers and words (<10: words in general). Verify statement regarding recurrence in patients whose follow-up was inadequate. Number operated with curative intent 44/46, should be clear. Have edited this section

h) Otherwise ok.

6. Discussion

a) Report predominately as "3rd person".

b) Where more than one study is implied in a statement, more than one reference should be cited e.g. several studies but only reference 17 is cited. Reference issue addressed

c) Please ensure that references are appearing sequentially. Done

d) Focused the discussion on findings from the study in relation with key issues covered/highlighted in the introduction (underlined) to avoid making it appear like a review article. Have made changes

e) Check grammar.

f) Otherwise ok, more so if it is kept as a simple audit. Shifted focus to purely descriptive study

7. Conclusion

a) Needs to be re-done. Have done so

b) It is too generic and not hinging on findings from the study. There are a number of significant conclusions which can be made (similarities/differences).

8. References

a) Happy in overall.

b) Check the sequence Mistake corrected