

**Sentinel Lymph Node Biopsy in a Resource Limited Setting: A Retrospective  
Comparison of Sentinel Lymph Node Biopsy before and after the introduction  
of SentiMag at an Academic Breast Unit**

by

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## **Acknowledgments**

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**Title: Sentinel Lymph Node Biopsy in a Resource Limited Setting: A Retrospective Comparison of Sentinel Lymph Node Biopsy before and after the introduction of SentiMag at an Academic Breast Unit**

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## **Sentinel Lymph Node Biopsy in a Resource Limited Setting: A Retrospective Comparison of Sentinel Lymph Node Biopsy before and after the introduction of SentiMag at an Academic Breast Unit**

### **Abstract**

**Background:** Sentinel lymph node biopsy (SLNB) is performed for the staging and prognostication of breast cancer in cases with a clinically and radiologically negative axilla. Using blue dye and a radioactive colloid injection is considered the gold standard for SLNB. This study aims to evaluate the SLNB outcomes before and after the introduction of SentiMag at an academic breast unit

**Methods:** A retrospective cohort study was performed comparing SLNBs done from (1 January 2017 to 31 December 2017) and (1 January 2018 to 31 December 2018). During 2017 all SLNBs were done with a nuclear medicine technique and in 2018 the Sentimag system was used.

**Results:** There was no difference between the 2 groups comparing age, T-stage, size of tumour, grade of tumour and molecular status. The only statistically significant difference found was more higher-grade tumours in the group where a nuclear medicine technique was used (2017)  $p=0.04$ . There was no difference in the type of surgery performed comparing mastectomy and breast conserving surgery rates between the 2 groups. There was an 11% increase in the number of patients who had a SLNB done with the SentiMag technique (2018). In 2017 42% (58/139) had a SLNB and in 2018 53% (59/112) had a SLNB

**Conclusion:** This result demonstrates the feasibility of the magnetic technique for SLNB in a resource constrained low- and middle-income country. This new method has none of the disadvantages of the standard technique and is promising as a safe and effective alternative in the absence of nuclear medicine facilities.

## Introduction

Cancer is increasing worldwide with low-and middle-income countries (LMIC) the worst affected. The rate of new cancers diagnosed as well as the mortality rate of cancer in LMICs is disproportionately higher compared to high-income countries.<sup>1</sup> Studies estimate that in by 2035 developing countries will harbor two thirds of the new cancer cases.<sup>2</sup> This projected increased burden of disease in LMIC demands that breast units position themselves to provide up-to-date surgical treatment of the axilla in women with early breast cancer.

Sentinel lymph node biopsy (SLNB) is a tool that is widely used for the staging and prognostication of breast cancer in patients who have a clinically and radiologically negative axilla. Using blue dye and a radioactive colloid injection is considered the gold standard for SLNB.<sup>3,4</sup> Using either blue dye or radioactive colloid injection individually leads to a detection rate of 85.6%, while using them together achieves a 96% detection rate.<sup>5</sup> Nuclear medicine techniques have several drawbacks including radiation exposure, nuclear medicine unit dependency and legislative control accompanying the use of radiopharmaceuticals. Hence, it is mostly used in centres with an active nuclear medicine department. An injectable magnetic tracer has become available, and it can be used as an alternative to SLNB. The magnetic tracer is a sterile aqueous suspension of superparamagnetic iron oxide (SPIO) particles with brownish colour that accumulate in the sentinel lymph nodes. This build-up is then identified using a handheld magnetometer (SentiMag®).<sup>6</sup> The main advantage of

SentiMag is that it is now possible to provide a sentinel node service away from nuclear medicine departments. In South Africa, access to nuclear medicine departments is limited as they are mostly situated in large academic hospitals making SLNB inaccessible to many women with breast cancer.

The study was conducted at Groote Schuur Hospital (GSH), an academic hospital in South Africa. Groote Schuur Hospital provides a centralized diagnostic breast cancer clinic and multidisciplinary team management for all patients diagnosed with breast cancer in the western part of Cape Town. An average of 550 new patients with breast cancer have been diagnosed between 2014 to 2017 with about 60% of patients presenting with early breast cancer.<sup>7</sup> The unit has been using a nuclear medicine technique to identify sentinel lymph nodes since 2001. In January 2018, the nuclear medicine technique was replaced by SentiMag for all SLNBs.

The study aimed to evaluate the SLNB outcomes of the newly introduced SentiMag technique in comparison to the standard nuclear medicine technique.

## **Methods**

A retrospective cohort study, which included all patients meeting the inclusion criteria managed by the Groote Schuur Hospital/University of Cape Town Breast Surgery Unit multidisciplinary team, from 1 January 2017 to 31 December 2018, was undertaken. The sample population was divided into 2 groups for comparison. The first group, named “nuclear medicine”, consisted of all patients who had surgery in 2017 and had an SLNB using a radioisotope, while the second group, named “SentiMag”, consisted of patients who had surgery in 2018 and had a SLNB using SPIO.

The data were retrospectively collected from patient notes, digital and paper records. All information was collected on a password-protected database. The

inclusion criteria were female patients, age 18 or older, who had breast surgery and axillary surgery for breast cancer at Groote Schuur Hospital and surrounding referral hospitals (New Somerset Hospital, Mitchells Plain Hospital and Victoria Hospital). Patients with ductal carcinoma in situ were included if they had axillary surgery. Patients were excluded from the study if they received neoadjuvant chemotherapy, had no axillary surgery, had non-epithelial breast cancer, or had incomplete records.

For sentinel node localization, patients receiving a nuclear medicine SLNB were injected with a radioactive tracer ( $^{99m}\text{Tc}$ ), the day before surgery. The injection was made subareolar in patients with non-palpable tumours and subcutaneously above the tumor in patients with palpable tumours. Lymphoscintigraphy was routinely performed, and the hottest node was marked on the skin of the axilla in the nuclear medicine department the day before surgery, as per local protocol. The timing and mode of administration of radioisotope were documented in the clinical records. Sentinel nodes were detected intraoperatively using a gamma probe. The magnetic technique was standardized for patients receiving a SentiMag SLNB. The operating surgeon injected a 5-ml solution, consisting of 2 ml of the magnetic tracer Sienna+ (Sysmex Europe GmbH, Hamburg, Germany) diluted with 3 ml of normal saline, into the retroareolar subcutaneous space. The solution was injected pre-operatively the day before surgery. During surgery, the surgeon used a handheld magnetometer SentiMag®, (Sysmex Europe GmbH, Hamburg, Germany) for skin localization of the sentinel lymph node. After incision, the surgeon removed all metal instruments from the operative field and replaced them with plastic retractors and forceps before the handheld magnetometer was used for sentinel node localization. Excision of nodes with the handheld magnetometer was undertaken by using the same cut-off as used for the gamma probe. Any node with a count of 10 % or more of the node with the

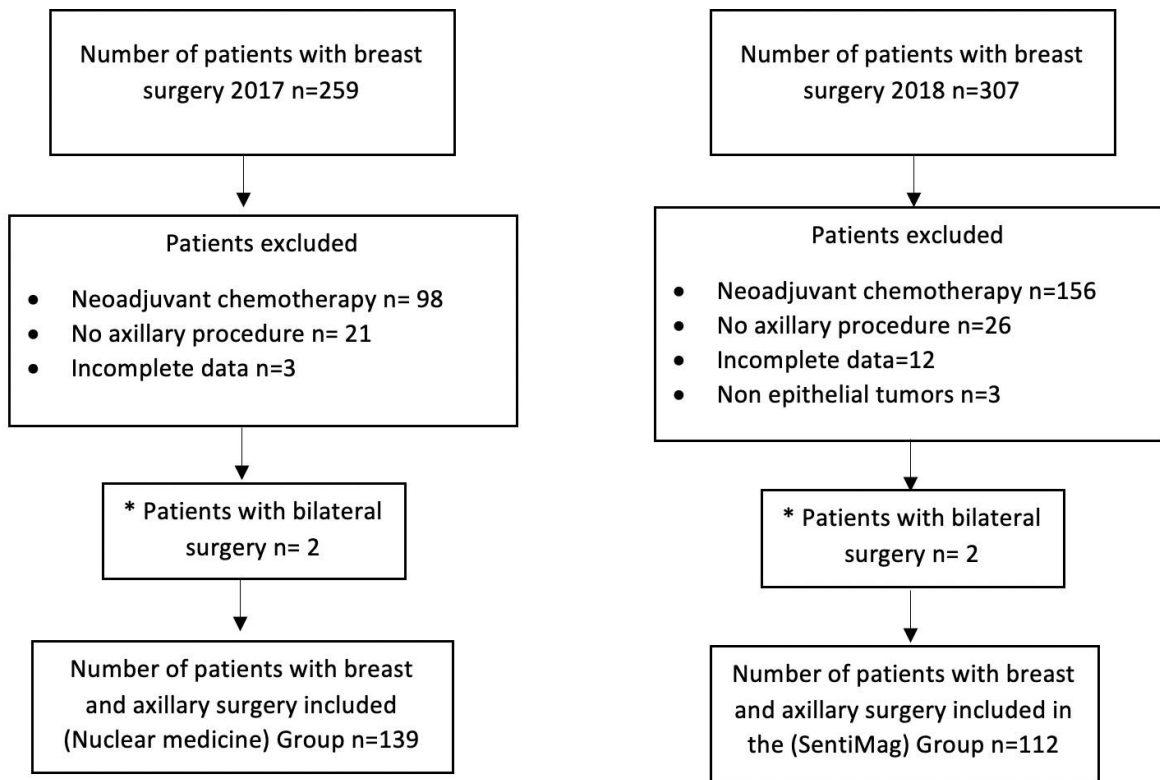
highest count was excised. Beyond four sentinel nodes, surgeons noted the background count and excised additional nodes only at their discretion. Any palpable nodes were also removed. All nodes were examined with hematoxylin-eosin staining on paraffin-embedded specimens.

Ethical approval for the study was received from the Human Research and Ethics Committee of the University of Cape Town (HREC number 199\2019). The data were analysed using STATA v14. Numerical data were summarized as means and medians and categorical data were summarized as proportions. A t-test was used to compare means and a Wilcoxon Ranksum test was performed to compare medians. For categorical data, a Fisher's exact test or a Chi-squared test was used as appropriate. A level of significance was set at a two-sided p-value of 0.05

## **Results**

After excluding patients not meeting the inclusion criteria and, considering patients that had bilateral surgery, 140 axillary procedures were performed in 2017 and 112 in 2018. Bilateral breast patients are having their axillae counted separately

Figure 1 represents the numbers of patients included.



\* Bilateral surgeries were counted as 2 procedures

Figure 1

The description of the 2 groups of patients is represented in Table 1. The analysis found no statistical difference between the 2 groups comparing age, T-stage of tumours, size of an invasive tumor or molecular status of the cancers. However, there was a statistical difference in the grade of the tumours, with more high-grade tumours in the Nuclear Medicine group (p=0.04).

Variable	2017 (Nuclear Medicine) n=139	2018 (SentiMag) n=112	P-value
<b>Age (years); median, (IQR)</b>	59 (49-65)	59 (49-67)	0.56
<b>T-stage</b>			
Tis	12	9	0.99
T1	43	36	
T2	69	54	
T3	15	13	
<b>Size of invasive tumour (mm); median (IQR)</b>	n=127 25 (15-35)	n=103 22 (15-30)	0.68
<b>Grade (invasive cancer)</b>			
I	15	22	0.04
II	74	62	
III	38	19	
<b>Hormone/HER-2 receptor status of invasive cancer</b>			
HR pos/HER-2neg	101	87	0.11
HR pos/HER-2 pos	11	5	
HR-/HER-pos	9	2	
Triple neg	6	9	

\* In situ carcinoma was excluded from size, grade, and hormone receptor status data

#### Table 1: Patient and tumour data

The 2 groups were also compared in terms of surgical data (Table 2). There was no difference in the type of breast or axillary surgery between the two groups. Although there was an 11% difference in the number of patients receiving an SLNB, with more patients receiving SLNBs in 2018, the results did not reach statistical significance. The results did not show a statistically significant difference between the 2 groups comparing the number of nodes removed when doing a SLNB (p=0.17)

Variable	2017 (Nuclear Medicine) n=139	2018 (SentiMag) n=112	P-value
<b>Breast Surgery</b> Mastectomy BCS	110 29	80 32	0.16
<b>Axillary Surgery</b> ANC SLNB	81 (58%) 58 (42%)	53 (47%) 59 (53%)	0.08
<b>SLNB</b>			
Mean number of nodes removed	3.9	4.7	0.17
Node Positive Node negative	16/58 (28%) 41/58 (72%)	9/59 (15%) 50/59 (85%)	0.09

**Table 2: Surgical data**

## Discussion

Sentinel node biopsy was first reported in the 1990s as an attempt to decrease the number of patients with no axillary metastasis receiving an axillary lymph node dissection (ALND).<sup>8</sup> This is referred to as overtreatment of the axilla and needs to be limited to try and decrease complications such as lymphoedema of the arm and sensory nerve deficit of the axilla and upper arm after an ALND.<sup>9</sup> Unfortunately, the current gold standard technique in SLNB, using a nuclear medicine tracer and a gamma probe, is not widely available due to resource constraints in low- and middle-income countries.<sup>10</sup> Therefore, new technologies with equivalent efficacy are constantly being researched to offer SLNB without the dependence on a nuclear medicine department. SentiMag is the most promising of the new technologies available and is already widely used around the world.

Several non-inferiority trials have been published in Europe comparing SPIO to a radioisotope. In 2013 a study by Douek M *et al*<sup>3</sup> on 160 women with breast cancer scheduled for SLNB, who were clinically and radiologically node negative found that

the identification rate was 95.0 % (152 of 160) with the standard technique and 94.4 % (151 of 160) with the magnetic technique. Of the 404 lymph nodes removed, 297 (74 %) were true sentinel nodes.<sup>3</sup> In the Central-European SentiMag study, Thill M *et al*<sup>11</sup> compared (99m) Technetium (Tc) with the magnetic technique, using SPIO (Sienna+®) for localization of SLNs. The results showed a detection rate per patient of 97.3% (146/150) for (99m) Tc vs. 98.0% (147/150) for SPIO. Their results indicate that SLNB using the magnetic technique can be performed easily, safely and equivalently in comparison to the radiotracer method.<sup>11</sup> Pinero-Madrone A *et al*<sup>12</sup> also compared the magnetic to a nuclear medicine technique for the detection of SLNs. They found that transcutaneous and intraoperative detection rates were 95.5% vs 97.2%, and 97.2% vs 97.8% for SentiMag and Gama Probe respectively (concordance rates > 97%). At the node level, intraoperative and ex-vivo detection rates were 92.5% vs 89.3% and 91.0% vs 86.3% for SM and GP respectively. Non-inferiority was proven comparing SentiMag to the Gamma probe.<sup>12</sup> The French SentiMag feasibility trial evaluated the localization of breast cancer SLN using superparamagnetic iron oxide particles in comparison to the standard technique (isotopes ± blue dye). They reported a SLN identification rate of 98.1% for both methods, 97.2% for Sienna+® and 95.4% for the standard technique. The concordance rate was 99.0% per patient and 97.4% per node. Forty-six patients (43.4%) had nodal involvement. Among involved SLNs, the concordance rate was 97.7% per patient and 98.1% per node.<sup>13</sup> Rubio IT *et al*<sup>14</sup> assessed the concordance between SPIO and the Tc 99 radiotracer. The detection rate by Tc 99 was successful in 113 (95.7%) of patients and by SPIO in 116 (98.3%). Concordance rates per patient between the techniques was 98.2%. The SLN was positive in 36 (30%) of patients. Of this, SLN positivity was detected by both techniques in 32 patients which indicates that detection of SLNs with SPIO allows for easy

identification of axillary nodes, at a frequency not inferior to the radiotracer.<sup>15</sup> Karakatsanis A *et al*<sup>16</sup>, in the Nordic SentiMag trial, compared the efficacy of SPIO as a tracer with Tc and patent blue and reported that SN detection rates were similar between standard technique and SPIO both per patient (97.1 vs. 97.6 %,  $p = 0.76$ ) as well as per node (91.3 vs. 93.3 %,  $p = 0.34$ ), something which was not affected by the presence of malignancy. Concordance rates were also consistently high (98.0 % per patient and 95.9 % per node).<sup>16</sup>

Although, not statistically significantly different, this study did demonstrate an increase in the number of patients who had an SLNB after the introduction of SentiMag. There was an 11% increase in the number of patients who had an SLNB done, from 42% before to 53% after the introduction of SentiMag. The increase in access can be explained because of the nuclear medicine department limiting the amount of SLNBs that can be performed on a surgery list to a maximum of two. This limitation of cases is due to the time available on the gamma cameras available at GSH to perform lymphoscintigraphy. The limitation in access to SLNB using nuclear medicine forced surgeons at GSH to perform an ALND, on patients with a clinically node negative axilla, at referring hospitals where more surgery lists are available, to manage waiting times. The SentiMag technique allowed the surgeons to increase the number of SLNB cases done on an operating list increasing the amount of SLNB cases that can be done at GSH. It would thus seem that technology that is not constrained by the access problems of a nuclear medicine technique, i.e., availability of nuclear medicine facilities and availability of radiopharmaceuticals, increases access to SLNB. Grigoryan *et al*<sup>17</sup> recently reported that only 29 out of 54 (53%) of African countries had access to nuclear medicine imaging with 16 countries having a single department for the whole country. Only 13 (24%) countries, mainly in the north and south of Africa

had more than one facility.<sup>17</sup> This lack of access to nuclear medicine facilities makes new techniques of doing SLNB without the use of radiopharmaceuticals very attractive. This study, therefore, confirms findings from the literature that SPIO can be easier to use without the restrictions in availability, use, manipulation, and disposal of radiopharmaceuticals.<sup>12,13,18,19</sup>

Other than access to a nuclear department the cost of the equipment needed to implement an SLNB service is one of the main factors hampering the establishment of an SLNB service in developing countries. To the best of our knowledge, no cost analysis has been done to compare SentiMag to a nuclear medicine technique. There is initial capital that needs to be spent to acquire the detection equipment for both procedures. The cost of SPIO and radiopharmaceuticals is similar. Man *et al*<sup>20</sup> reported that the following all need to be accounted for in calculating the cost of a nuclear medicine SLNB service; day admission for injection of the radiopharmaceutical, specially arranged specimen transportation as per local risk management protocol, annual on-site contamination tests and monthly calibration of pocket dosimeters all at extra cost. They estimated that by using SPIO alone \$22,300 per year can be saved using SPIO compared to radiopharmaceuticals.<sup>20</sup>

The study did not show a higher nodal retrieval rate between the Nuclear medicine and Sentimag groups. The mean number of nodes removed using the nuclear medicine technique was 3.9 compared to 4.7 (p=0.17) in the patients who had the magnetic procedure. The results agree with current literature, many authors found that SLNB using SPIO resulted in a similar number of nodes retrieved compared to Tc. However, Rubio I *et al*<sup>14</sup>, retrieved more nodes in the SPIO group.

<b>Study (Ref.)</b>	<b>Number of nodes removed using Tc (mean)</b>	<b>Number if nodes removed using SPIO (mean)</b>	<b>P-Value</b>
Douek et al (2013) <sup>3</sup>	1.9	2.0	NS
Thill et al (2015) <sup>11</sup>	1.8	1.9	NS
Rubio et al (2015) <sup>14</sup>	1.77	2.2	p = 0.001
Karakatsanis et al (2016) <sup>16</sup>	1.8	1.8	NS
Houpeau et al (2016) <sup>13</sup>	1.8	1.9	NS

It is currently not known why some surgeons harvest more nodes using the SentiMag procedure. Rubio *et al*<sup>14</sup> speculated that it could be explained by a learning curve in using the new tracer agent. The SentiMag technique is different from the nuclear medicine technique in that plastic instruments need to be used during the time the magnetometer is used to prevent interference. Another reason for the increase in the number of lymph nodes removed could be due to the difference in the size of the tracer particles leading to the tracer being taken up differently by the axillary lymph nodes.

The major limitation of this study is the retrospective nature of data collection which can lead to selection bias. A strength is that it not just reports on the results of the SentiMag procedure in isolation but rather compares the new technique to the previous standard of care. Further studies are needed to add to the already considerable amount of data supporting SentiMag as a viable alternative to conventional methods.

## **Conclusion**

This study demonstrated the feasibility of the magnetic technique for SLNB in a resource limited setting. The results from this study, along with the accumulating evidence from the literature, are practice changing. This new method has none of the disadvantages of the standard technique and is promising as a safe and effective alternative in the absence of nuclear medicine facilities, making it ideal for SLNB in resource-constrained settings.

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05 April 2019

**HREC REF: 199/2019**

**Dr F Malherbe**  
Surgery  
J-Floor, OMB

Dear Dr Malherbe

**PROJECT TITLE: REDUCING THE NUMBER OF UNNECESSARY AXILLARY LYMPH NODE DISSECTIONS THROUGH THE USE OF SENTIMAG**

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 30 April 2020.**

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.

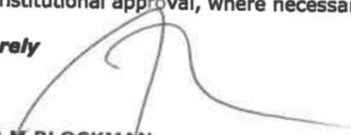
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Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

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*Yours sincerely*


  
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**CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE**  
Federal Wide Assurance Number: FWA00001637.  
Institutional Review Board (IRB) number: IRB00001938  
NHREC-registration number: REC-210208-007

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

HREC 199/2019

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**Principal Investigator to complete the following:**

#### 1. Protocol information

Date (when submitting this form)	10/08/2021		
HREC REF Number	199/2019	Current Ethics Approval was granted until	30/04/2020
Protocol title	REDUCING THE NUMBER OF UNNECESSARY AXILLARY LYMPH NODE DISSECTIONS THROUGH THE USE OF SENTIMAG		
Principal Investigator	F Malherbe		
Department / Office Internal Mail Address	Department of Surgery J Floor, OMB, Groote Schuur Hospital		
1.1 Does this protocol receive US Federal funding?		<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No



#### 2. Protocol status (tick ✓)

<input type="checkbox"/>	Research-related activities are ongoing
<input checked="" type="checkbox"/>	Data collection is complete, data analysis only
Please indicate (in the block below) the titles and HREC reference numbers of any projects currently making use of the Database/registry/repository.	

#### 3. Protocol summary

Total number of records or specimens collected, reviewed or stored since the original approval	
Total number of records or specimens collected, reviewed or stored since last progress report	
Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report.	<input type="checkbox"/> Yes <input type="checkbox"/> No

#### 4. Signature

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- (ii) drafting or critical revision for important intellectual content; and
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Authors are advised to involve medical statisticians at the protocol stage of their research project: to plan sample size, and the selection of appropriate statistical tests for analysis and presentation.

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The rationale for analysis based on racio-ethnic-cultural categorisation should be indicated.

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Shorter items are more likely to be accepted for publication, owing to space constraints and reader preferences.

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Original articles on research relevant to surgery should not exceed 3 000 words, no more than 30 references, with up to 6 tables or figures. A structured abstract under the following headings, Background, Methods, Results, and Conclusions is a requirement and should not exceed 250 words.

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How to do it submissions should address a practical aspect of surgical or interventional (endoscopic or radiological) patient management in which a best practice technique or method to advance optimal patient management is presented in a standardised format. The submission should be structured with a short contextual introduction focussing on the indications for the procedure, followed by numbered sequential points that explain and

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**Journal references:** Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. *Stat Med* 1998;289(1):350-355. [<http://dx.doi.org/10.1000/hgjr.182>] [PMID: 2764753]

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