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Electrochemotherapy for the treatment of primary basal cell carcinoma; A randomised control trial comparing electrochemotherapy and surgery with five year follow up

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ABSTRACT

Basal cell carcinoma (BCC) are the commonest cutaneous malignancy and incidence continues to increase. There is a need to expand the therapeutic toolbox to increase options for patients that are unsuitable for or unwilling to undergo the current therapies.

Electrochemotherapy (ECT) is a technique where cells are temporarily permeabilized after exposure to a brief pulsed electrical field and combined with low dose chemotherapeutics to ablate malignancies. It is a simple technique causing minimal damage to the surrounding healthy tissue and has the potential to avoid the need for complex reconstruction. ECT is an established treatment for skin metastases but its role as a primary treatment modality is not demonstrated.

A prospective randomised control trial evaluating ECT against the gold standard of treatment, Surgery, was performed for patients with primary BCC and patients followed for 5 years. All lesions treated with ECT (n = 69) responded although 8/69 (12%) needed a second treatment to ensure a complete response. All surgical lesions (n = 48) showed histological evidence of complete excision with 2/48 (4%) undergoing a second excision. At 5 years, in the surgical arm there was no evidence of recurrence in 39/40 (97.5%) lesions with 1/40 (2.5%) confirmed recurrence. In the ECT arm there was no evidence of recurrence in 42/48 lesions (87.5%). There was 5 confirmed recurrences. These groups show statistical equivalence in this non inferiority study design (p = 0.33).

ECT is an effective and durable treatment option for primary BCC and should be considered as part of the armamentarium of options available.

Introduction

Basal cell carcinoma represents an ongoing and evolving clinical challenge. Worldwide, there is an increasing number due to the ageing population, along with increasing recreational sun exposure. The majority of BCC are diagnosed in the head and neck region in patients between 60 and 80 years old [1,2]. The gold standard for treatment of BCC is surgical excision although a wide variety of treatment options are available for lesions unsuited to surgery. Electro-permeablisation and intra lesional chemotherapy is a rapid and simple treatment that could serve as an adjunct in the treatment options for BCC, diminishing the need for surgery [3]. This is especially pertinent in those with significant co morbidities [4].

Electroporation is a simple phenomenon, which occurs when the cell membrane is temporarily destabilised by the local application of an electrical pulse. This results in pores being created on the cell surface which allows drugs present locally to enter the cell by passive diffusion [5]. When electroporation is combined with an otherwise impermeant or poorly permeant anticancer drug, such as bleomycin, the treatment is referred to as Electrochemotherapy (ECT) and results in a potent localized cytotoxic effect [1–3,6] ECT is being increasingly used in the treatment of cutaneous malignancies in patients in whom previous standard of care options were

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unsuccessful and as a treatment for lesions recalcitrant to chemotherapy or radiotherapy [7,8].

Early published data demonstrated the potential of ECT as a locally ablative treatment option for BCC [9]. Meta-analysis of the efficacy of ECT suggested that BCC appeared overall to respond better to ECT than other cutaneous malignancy histiotypes [6]. The National Institute for health and clinical excellence [10] deemed that ECT was a safe treatment for primary BCC but remarked on the limited evidence available. Our own experience in treating BCC in difficult anatomical locations in patients deemed unsuitable for surgery due to co-morbidities supported the potential efficiency of ECT in the treatment of BCC [11].

In any treatment initial removal of the lesion is the initial primary objective, however ensuring that the patient remains disease free over time is the important arbiter of the overall usefulness. We aimed to assess the effectiveness of ECT as a treatment for primary BCC in a randomised control trial with the current gold standard of treatment surgery as the comparator and assess durability of response. It is not at this stage a comparator for routine day to day clinical practice, although potentially there is a defined cohort of patients that would benefit from this treatment in routine practice [12]. This represents the first reported randomised control trial with ECT used as a treatment for a primary cutaneous tumour with a completed 5 year follow up.

Methods

A parallel group non inferiority trial was established to assess the efficiency of ECT as an option for the treatment of primary BCC and was powered accordingly [13]. The trial was conducted with Ethical approval from the Cork University Hospitals Research and Ethics Committee and prospectively registered with EURDACT **EudraCT Number:** 2010- 019260−37 and complies with the recommended reporting standards for trials in ECT [14]. The trial was set up as a non-inferiority trial with the non-inferiority margin set at 8%, [15].

Patient selection

Patients with Biopsy proven Primary BCC with no clinical evidence of deep structural involvement were assessed and recruited from the outpatient clinic. Initial assessment included suitability for ECT and ruled out contraindication to Bleomycin and willingness to undergo follow up over a 5 year period. Full inclusion and exclusion criteria are detailed in Supplemental Fig. 1. Randomisation was performed using the sealed envelope method after successful enrolment in the trial.

Surgery

Surgery was performed according to standard of care. Procedures were carried out under general or local anaesthesia, the lesions were removed with 4 mm margin of healthy skin [15,16] and wounds closed primarily or using a skin flap or using a skin graft as deemed appropriate. The choice of anaesthetic was based on clinical and patient factors.

Electrochemotherapy

The standard operating procedures for cutaneous application of Electrochemotherapy with Bleomycin are established and were employed in this study. Procedures were performed under local anaesthesia and conscious sedation as a day case. The intratumoural dose of Bleomycin was calculated according to the size of each lesion according to treatment guidelines [7]. The peripheral and deep margins were covered as described in the European Standard Operating Procedures [17] Electric pulses were generated by the Cliniporator (IGEA, Carpi, Italy) (8 square wave pulses 1000 V/cm for 100 μs at 5 kHz) and were delivered into the tumours either the parallel row electrode or the hexagonal electrode. Patients were assessed for response at 30 days. A second session of Electrochemotherapy was offered to those showing partial response only at 60 days. If no improvement was noted at 3 months after the re-treatment or the result unsatisfactory, the study protocol would have proceeded to surgical excision. This, however, was not needed.

Follow up

Patients were followed up for the period of 5 years after the treatment. They were seen by a clinician 30, 60, 90, 180 days, 1, 2, 3 and 5 years after treatment. During each visit patients were examined, the treated area assessed and photographs of the treated area taken. Any suggestion of clinical recurrence was noted and excisional biopsy planned for definitive histological evidence.

Results

Demographics

233 patients with a newly diagnosed BCC were assessed for suitability for the trial of whom 99 were enrolled and randomised. (ECT 52 patients; Surgery 48 patients). Patient enrolment and follow up is presented in Fig. 1. Demographics of those enrolled is presented in Fig. 2a which demonstrates homogeny of populations in terms of average age, age range and sex. The average size of the lesions was 1.7 cm^2 for lesions treated by ECT (Range 0.24−10.5) and 1.4 cm^2 (Range 0.25−5) lesions treated by Surgery. Fig. 2b demonstrates the range of basal cell carcinoma histiotypes treated in the two comparative arms.

In the Electrochemotherapy group, 52 people were randomised but only 50 treated as 2 withdrew after randomisation and prior to treatment. 50 patients with 65 lesions were treated. All were treated with a combination of local anaesthetic and sedation. All received intra-tumoural bleomycin with an average of 1633 IU (Range 500−5000). 47 patients were treated with type 2 parallel row electrodes and 3 with Type 3 hexagonal electrodes (Fig. 3).

45/50 patients treated ECT were able to be followed up to assess completeness of response. 3 patients were excluded as lesions were not histologically BCC, 2 Elderly patients were treated and then withdrew.

In the Surgical group, 47/52 lesions in 42/48 patients were followed up to 3 months. Of those that withdrew 5 enrolled then withdrew prior to treatment and 1was lost to follow up before 3 months. For those lesions included in the follow up 44 underwent excision under local anaesthetic with 3 undergoing general anaesthetic. Primary closure of the defect was performed in 36/47 lesions with 8/47 requiring local flap reconstruction and 3/37 requiring a skin graft (these were the 3 patients undergoing general anaesthetic).

Response to treatment

Overall, All patients in the study responded to their allocated treatment. In the Elctrochemotherapy group patients 60/65 lesions or 40/45 (86%) patients demonstrated a complete response assessed at 60 days post treatment. The remaining 5 patients underwent a second treatment as outlined in the study protocol, all (100% of lesions) demonstrating a complete response after a second treatment. In the surgical arm, 39/41 patients had complete

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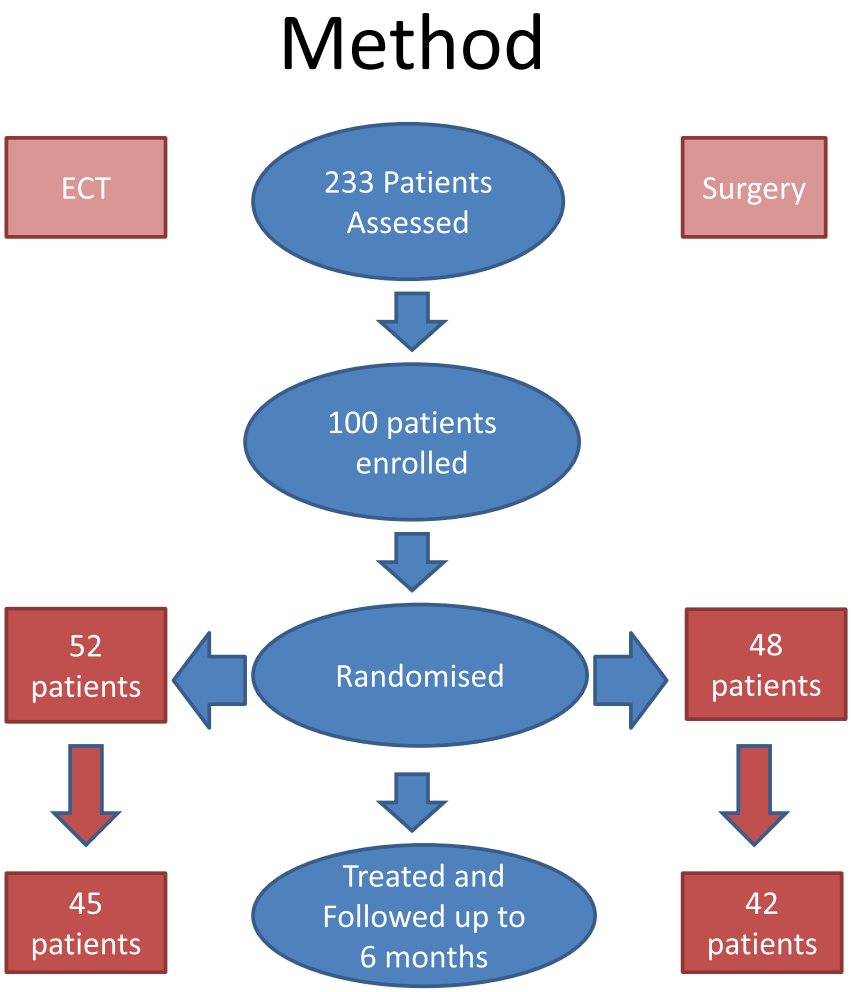

Fig. 1. Recruitment and randomisation algorithm. Patients were followed out to six months to demonstrate effective complete response to Electrochemotherapy and then further followed for 5 years after treatment to assess durability of response.

histological clearance after primary excision. The remaining two patients underwent further wider excision to achieve complete histological clearance. Thus at the beginning of the observation period a complete response was demonstrated in all patients recruited for the trial (Fig. 4).

Adverse reactions

23 adverse reactions were reported in total following treatment, all grade 1 or 2. In the surgical group there were 6 reported infections requiring antibiotics and 2 cases of reported erythema and swelling around the incisions. In the ECT group there were 5 reported infections requiring antibiotics, 4 incidences of superficial ulceration following treatment, 3 reports of erythema, 1 reported incidence of pain. 2 events were reported in the ECT group probably unrelated to treatment including 3 days of headaches and 2 days of loosened stool following treatment. These are reported in Supplemental Table 2.

Follow up and recurrence

Patients were followed out as per the trial protocol over a 5 year period. During the period of follow up there were inevitable patients that withdrew from the trial or were lost to follow up. Overall in the surgery group, 36/42 (85%) patients with 40/47 (85.2%) lesions completed the follow up period. There was one recurrence in this group (1/36 patients and 1/40 lesions). The overall complete response rate in the surgical group was 39/40 (97.5%). In the ECT group, 37/45 (82%) patients with 47/65 (72%) lesions completed the follow up. There were 5 recurrences in this group. The overall complete response rate at 5 years was 42/47 (89.4%).

If intention to treat analysis is performed there was a recurrence rate of 1/52 (1.9%) in the surgical group and 5/67 (7.5%) in the ECT group ($p = 0.33$).

Discussion

The local tissue destruction caused by an unchecked BCC can be extensive [18]. As the incidence of BCC increases there will be an increasing number of patients either unsuitable or unwilling to undergo surgical excision and as such a wide, effective and long term treatment armamentarium is required. Here we describe a long term follow up of patients with primary BCC treated with ECT that demonstrate it as an effective treatment modality with good durable response rates. This trial represents the first randomised control trial using Electrochemotherapy as a treatment of primary BCC as well as the first to report long term follow up on a cohort of patients. Recent cumulative analysis over a 10 year period confirms

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a)

	ECT	SURGERY
Enrolled	52	48
Av Age	66.8±13.0	63.8 ± 12.6
Range	24-92	37-91
M	25	24
F	27	23
Size cm^2	1.7 (0.24-10.5)	1.4 (0.25-5)

b)

Subtype	ECT	Surgery
Nodular	19	22
Nodular/ Inflitrative	14	5
Morpheic	2	4
Undefined	13	7
Superficial	4	4
Infiltrative	0	4
Ulcerative	0	2
Total Patients	52	48

Fig. 2. Demographics and Histological subtypes of BCC. Fig. 2a demonstrates the demographics of the patients recruited including average size of lesion and ranges of lesions treated. Fig. 2b shows the histological subtype of BCC treated demonstrating the expected wide range of histological sub types encountered and treated.

a)

	ECT	Surgery
Patients Treated	50	42
Single Lesion	38	37
2 Lesions	9	4
3 Lesions	2	1
7 lesions	1	
Total lesions	69	48

b)

ECT

- 50 Treated
  - 50 LA and Sedation
- Bleomycin
  - 50 Intratumoural
  - 1653 IU (Range 500-5000)
- Needle Type
  - 47 Type 2 Parallel
  - 3 Type 3 Hexagonal

Surgery

- 52 Treated
  - 41 Primary Closure
  - 8Local Flap
  - 3 Skin Graft
- Anaesthetics
  - 38 Local Anaesthetic
  - 3 General Anaesthetic

Fig. 3. Total number of lesions treated and details of treatment type. Fig. 3a demonstrates the distribution of lesions across the patients treated. Fig. 3b demonstrates the details of the treatment specifics for those treated.

that smaller primary BCC treated with intratumoural bleomycin are most likely to respond to ECT in support of our findings [12].

There are many potential advantages to surgical excision of a primary lesion, in order to both confirm diagnosis and ensure completeness of excision. Realistically it is likely that there will remain many instances in which the reassurance of excision with confirmed histological clearance will remain the preferred treatment modality. However there are similarly many patient or lesion specific characteristics that confer advantage on a locally ablative treatment [19]. In many instances, non-surgical options may be considered with acceptable cure rates and cosmetic results; Radiotherapy is a time consuming modality and is not a preferred treatment option close to the orbit due to the risk of orbital damage [16]. Treatment of recurrent or recalcitrant lesions may be more difficult in previously irradiated tissue. Photodynamic therapy or topically applied chemotherapeutic agents, may also be considered but are contra-indicated in high-risk lesions and are limited by poorer response rates and the scarcity of long-term data on recurrence [16,20].

The initial impression on the use of ECT as a treatment for primary BCC was that these lesions remained at higher risk of recurrence [9,21]. However, there was much heterogeneity in delivery and treatment protocols prior to publication of European standard operating procedures in 2006 after multinational phase 2 trial [17]. Later Systematic review of the efficiency of ECT confirmed an overall very high objective and complete response rates for BCC treated with ECT, demonstrating a Complete Response rates of 88% after single treatment and an Objective Response rate of 100% [6]. A multinational trial assessing the efficacy of ECT in head and neck tumours, including BCC confirms small, primary, and treatment-naive carcinomas responded best [22]. Our own experience demonstrated the utility of using ECT to treat BCC in those either unsuitable or unwilling to undergo surgical resection and staged reconstruction particularly in the naso-ocular region [11]. There remains only one objective comparison for ECT as compared to other ablative treatments, comparing its efficacy with other ablative techniques for the treatment of cutaneous metastasis in which it's positive efficacy is demonstrated [8].

Electrochemotherapy has been successfully demonstrated across a wide range of tumour histiotypes [23] with high levels of efficiency, although BCC in particular appear to be highly responsive [6]. The mechanism for this is as yet not understood. In part, size of the lesion is relevant, wherein lesions less than 3 cm^2 consistently show higher response rates [4,6]. The average size of lesion in both groups was within this bracket. Although other factors are also likely to contribute. In general, BCC are overall very responsive to treatment and do not necessarily recur even in the event of incomplete excision [19,24]. The reasons remain poorly understood, although excision of biopsy proven BCC can sometimes result in no residual tumour demonstrated upon subsequent biopsy [25], one speculative mechanism is the potential for an immune mediated event causing tumour regression during wound healing [26,27]. This was not assessed in this study although ECT has been associated with other immune mediated

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Response to Treatment

- Treatment

Patients	ECT	Surgery
Single treatment	40 (86%)	39 (95%)
2nd Treatment	5 (14%)	2 (5%)

Lesions	ECT	Surgery
Single treatment	57 (88%)	46 (96%)
2nd Treatment	8 (12%)	2 (4%)

- Complete Response

Patients	ECT	Surgery
Single Treatment	40 (86%)	39 (95%)
2nd Treatment	45(100%)	41 (100%)

Lesions	ECT	Surgery
Single Treatment	61 (88%)	46 (96%)
2nd Treatment	69 (100%)	48 (100%)

Fig. 4. Response to treatment. Fig. 4a shows the response to treatment per patient and per lesion. The majority of patients in both cohorts required a single treatment. In the ECT cohort those not demonstrating complete response at 3 months were offered a second treatment to ensure completeness of response. Fig. 4b demonstrates complete response rates after a single or second treatment. All patients included in this study in both arms demonstrates a complete response to treatment assessed histologically for the surgical arm and clinically for the ECT treated arm at 6 months after recruitment.

tumour regression [28], raising this as a potential contributor to the overall efficiency seen.

Recurrence rates are crucial to establishing ECT as a treatment for BCC and, in particular, in anatomically sensitive sites. This trial was powered as a non-inferiority study using surgical excision as the gold standard. We acknowledge that the overall recurrence free incidence at 5 years was within the treatment range of the other ablative treatment choices such as radiotherapy [29,30], Curettage [31] and topical therapies [16,32] as opposed to the expected recurrence free incidence for surgery. However ECT is demonstrated as both an effective treatment which is for the most part durable. Similarly, this trial was not at this stage designed as a comparator for practical day to day practice. This initial first step is crucial in the development of ECT as an integral part of the treatment tool box and we acknowledge the current limitations of the treatment as given in its current form. The particular advantages of ECT is twofold; one it appears to be well tolerated in patients with significant co-morbidities that might otherwise be less than ideal candidates for resection and staged reconstruction [11], secondly as a procedure it is well tolerated even in tissue that has been subject to previous treatments such as surgery or radiotherapy [4], side effects are relatively rare [6] and the dose of the chemotherapeutic agent can be minimized with intra-tumoural injection. Bleomycin can be injected either intratumourally and intravenously during electrochemotherapy. The initial results of the ESOPE trial showed no difference in overall response rate between IV and IT Bleomycin [17]. Intratumoural bleomycin was chosen in this study as this allowed for a smaller total bleomycin dose and mitigates the small risks of intravenous administration of bleomycin. The updated standard operating procedures for the use of electrochemotherapy (have subsequently endorsed this approach suggesting that for smaller and fewer lesions an IT approach should be considered [7].

This cohort of patients had their ECT delivered under a combination of local anaesthetic and sedation in order to better tolerate any myoclonic reaction during pulse delivery. Further refinement of the delivery parameters used to deliver effective electroporation are under instigation in order to be able to perform this procedure without sedation and as a single session office based procedure as refined pulse parameters can induce electroporation without causing myoclonic thus reducing the need for sedation. Refinements that abrogate the need for a chemotherapeutic are also under investigation; Supra physiological doses of Calcium have been used in association with electroporation to achieve comparable results to electroporation with bleomycin using Calcium in supra physiological doses [33] due to cellular necrosis from severe ATP depletion. This regimen will be used in what we are terming “painless electroporation” to treat primary BCC in our next phase clinical trial. Similarly this trial was not established to look for a cost benefit in treatment with ECT, however it is anticipated that the treatment costs will likely fall as the protocol continues to be refined.

The vast majority of patients undergoing ECT achieved a complete response after a single session, however 14% still required a second treatment. This comparably higher than in the surgery group. The study protocol allowed for 2 ECT treatment sessions in the event of an initial partial response and all patients achieved a complete response after these two sessions. This second treatment according to protocol and patient selection may account for the complete level of responses reported as opposed to other works which show a high but not complete level of response [6,12,22] and is comparable to other series in reporting the treatment response to BCC [22]. Nonetheless, the need for a second treatment in a sizeable fraction of the treatment population is an area that requires further investigation and improvement if this treatment is to be successfully translated into a more frequently considered primary option.

This minimally invasive technique is an effective adjunct to surgical excision in the treatment of basal cell carcinoma, leading to good resolution with highly acceptable long term durability of treatment. It may be particularly useful in the management of BCC in patients with multiple co morbidities [12], or as an adjunct to standard surgical in anatomically sensitive areas [11,22]. In our practice ECT is now considered in these few patients where surgery may be challenging or potentially reconstruction can be avoided by using this ablative technique. As such we consider the use of ECT in naso-ocular areas which may need multistage reconstruction or on exophytic lower limb lesions that wish to avoid donor site issues. ECT may also gain prominence as a treatment for the multiple lesions that occur in Gorlin Goltz Syndrome [34].

The ideal treatment for BCC's should yield satisfactory complete resolution rates, with satisfactory patient experience, minimal side effect profile and adequate cosmesis. These attributes are demonstrated with ECT for BCC [12]. This first prospective study reporting 5 year outcome data for the treatment of primary BCC with Electrochemotherapy confirms the efficiency and durability of this

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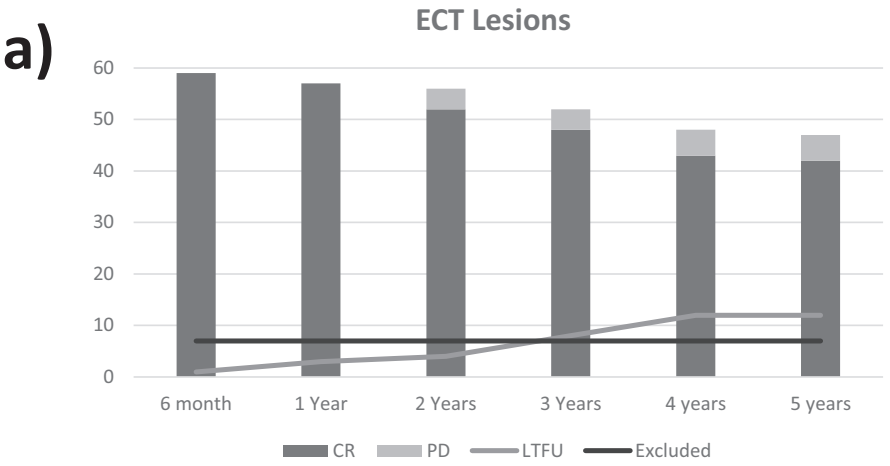
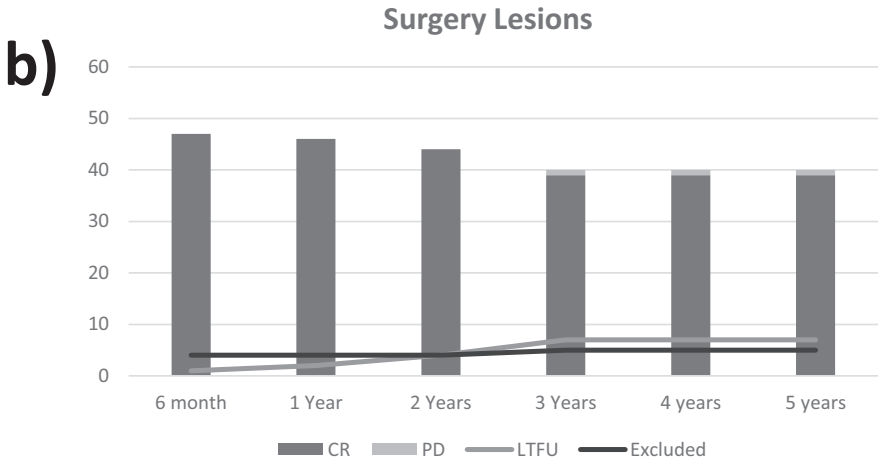


LESIONS						
ECT	6 month	1 Year	2 Years	3 Years	4 years	5 years
CR	59	57	52	48	43	42
PD	0	0	4	4	5	5
LTFU	1	3	4	8	12	12
Excluded	7	7	7	7	7	7



LESIONS						
Surgery	6 month	1 Year	2 Years	3 Years	4 years	5 years
CR	47	46	44	39	39	39
PD	0	0	0	1	1	1
LTFU	1	2	4	7	7	7
Excluded	4	4	4	5	5	5

Fig. 5. Durability of Response for treated lesions. Fig. 5 demonstrates the follow up profile for lesions treated with surgery or with ECT over time. Fig. 5a gives the results for lesions treated with ECT and Fig. 5b gives the results for lesions treated with surgical excision. The complete responders are shown in the dark bar of the chart and those with recurrence are in the lighter bar. Those excluded due incomplete initial evaluation of response and those lost to follow up are shown linearly.

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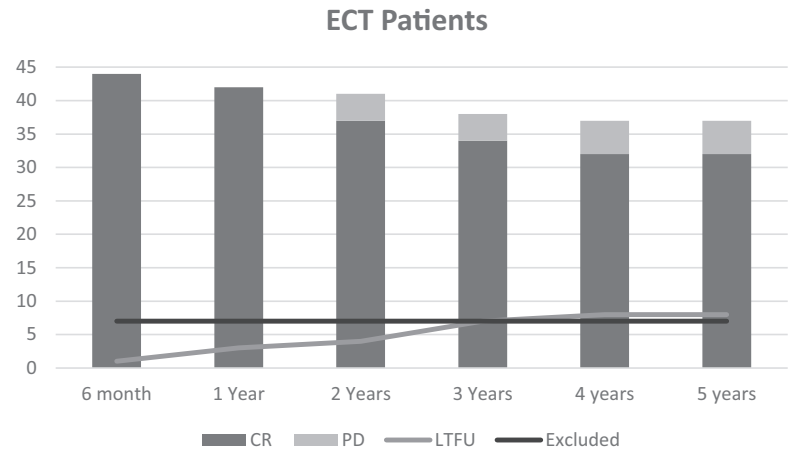
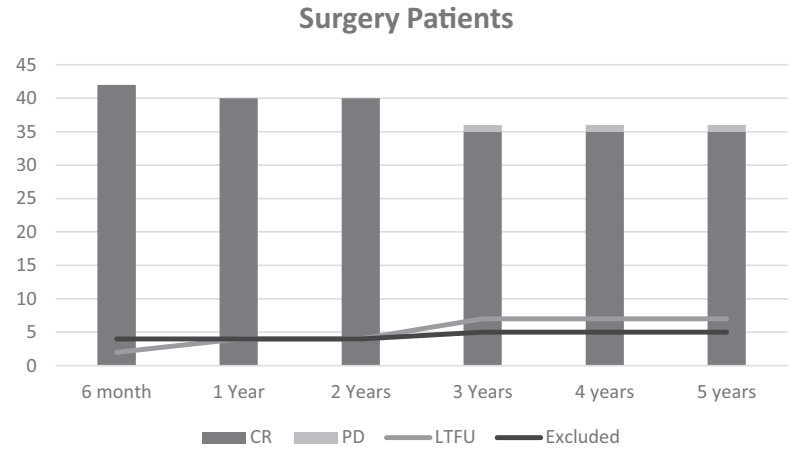
a)



PATIENTS						
ECT	6 month	1 Year	2 Years	3 Years	4 years	5 years
CR	44	42	37	34	32	32
PD	0	0	4	4	5	5
LTFU	1	3	4	7	8	8
Excluded	7	7	7	7	7	7

b)



PATIENTS						
Surgery	6 month	1 Year	2 Years	3 Years	4 years	5 years
CR	42	40	40	35	35	35
PD	0	0	0	1	1	1
LTFU	2	4	4	7	7	7
Excluded	4	4	4	5	5	5

Fig. 6. Durability of Response for treated patients. Fig. 6 demonstrates the follow up profile for patients treated with surgery or with ECT over time. Fig. 5a gives the results for patients treated with ECT and Fig. 5b gives the results for patients treated with surgical excision. The complete responders are shown in the dark bar of the chart and those with recurrence are in the lighter bar. Those excluded due incomplete initial evaluation of response and those lost to follow up are shown linearly.

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treatment option.

Declaration of competing interest

AJPC, DS, SS and MB have received travel subsidy from IGEA. IGEA had no contribution to the design, conduct or results reporting of this study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.11.509.

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