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Original Article

European e-Delphi process to define expert consensus on electrochemotherapy treatment indications, procedural aspects, and quality indicators in melanoma

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Abstract

Background: Skin metastases are an important co-morbidity in melanoma. Despite broad adoption, electrochemotherapy implementation is hindered by a lack of treatment indications, uncertainty regarding procedural aspects, and the absence of quality indicators. An expert consensus may harmonize the approach among centres and facilitate comparison with other therapies.

Methods: An interdisciplinary panel was recruited for a three-round e-Delphi survey. A literature-based 113-item questionnaire was proposed to 160 professionals from 53 European centres. Participants rated each item for relevance and degree of agreement on a five-point Likert scale, and received anonymous controlled feedback to allow revision. The items that reached concordant agreement in two successive iterations were included in the final consensus list. In the third round, quality indicator benchmarks were defined using a real-time Delphi method.

Results: The initial working group included 122 respondents, of whom 100 (82 per cent) completed the first round, thus qualifying for inclusion in the expert panel (49 surgeons, 29 dermatologists, 15 medical oncologists, three radiotherapists, two nurse specialists, two clinician scientists). The completion rate was 97 per cent (97 of 100) and 93 per cent (90 of 97) in the second and third rounds respectively. The final consensus list included 54 statements with benchmarks (treatment indications, (37); procedural aspects, (1); quality indicators, (16)).

Conclusion: An expert panel achieved consensus on the use of electrochemotherapy in melanoma, with a core set of statements providing general direction to electrochemotherapy users to refine indications, align clinical practices, and promote quality assurance programmes and local audits. The residual controversial topics set future research priorities to improve patient care.

Introduction

Variation in surgical procedures is common, but patient outcomes may be unacceptably heterogeneous[1]. Skin involvement affects 10–18 per cent of patients with melanoma and almost 50 per cent of those with metastatic disease[2–5], with remarkable implications on quality of life (QoL)[6].

Of note, the management of in-transit/superficially metastatic melanoma lies at the crossroad of different therapies, that is locoregional chemotherapy, injectable therapies, and systemic treatment. Among locoregional therapies, isolated limb perfusion (ILP) provides an overall response rate (ORR) of 80 per cent, with a complete response rate (CRR) of 60 per cent[7], whereas isolated limb infusion (ILI) ensures ORRs and CRRs of 53–75 and 29–33 per cent respectively[7,8]. Among injectable therapies, oncolytic immunotherapy with talimogene laherparepvec (T-VEC) is associated with a lower ORR and CRR (31.5 and 16.9 per cent); however, it does not require general anaesthesia, can be repeated, and, interestingly, the subgroup of complete responders have a survival benefit (88.5 per cent at 5 years)[9]. Furthermore, evidence shows that T-VEC is effective as a rescue option for patients who progress after checkpoint inhibition (in-field ORR 51 per cent, CRR 37 per cent)[10]. Despite a lack of specific information on patients with in-transit disease in registration trials[11], three retrospective studies[12–14] that included 54, 287, and 70 patients with superficially metastatic melanoma treated with systemic anti-CTLA-4 or anti-PD1 (programmed death protein 1) agents showed an ORR of 31.7, 54, and 56 per cent, respectively (CRR 12.9, 26, and 36 per cent). As a result, immunotherapy is recommended in some guidelines as the first option for patients with melanoma who could be eligible for locoregional therapies.

Comparisons of immunotherapy experiences and other therapeutic approaches are hampered by the heterogeneity of populations, disease burden, criteria of response and toxicity assessment, and information on previous/subsequent oncological treatments. In general, early application is associated with more sustained response rates[15,16]. Nonetheless, adopting combined strategies to achieve a complete response (for example ILI followed by surgical resection) may improve local tumour control and patient survival[17]. Future studies in patients with in-transit/superficially metastatic melanoma should adopt shared criteria to describe disease burden, patterns of spread, and tumour kinetics. They should also focus on reliable risk stratification biomarkers[18], and test combination approaches to turn immunologically 'cold' tumours into 'hot' tumours[19,20].

Since 2006, electrochemotherapy (ECT), the co-delivered administration of bleomycin or cisplatin and targeted electric pulses, has been introduced among skin-directed therapies to palliate primary or superficially metastatic skin cancer[21]. Usability[22,23], efficacy[24–26], and safety[27,28] are all well documented, along with a beneficial impact on QoL[29–31]. On this basis, the National Institute for Health Care and Excellence (NICE)[32] has endorsed ECT application, provided that a multidisciplinary team selects patients and that outcomes are sent to the International Network for Sharing Practices of ECT (InspECT) registry. Despite the availability of procedure-specific (European Standard Operating Procedures for ECT, ESOPE[22,23]) and melanoma-specific guidelines[33], controversy persists regarding patient selection, treatment application, and outcome assessment. Because of this, variation exists between centres in ECT practice, precluding reliable evaluations and comparisons[34].

Regarding treatment indications, there is uncertainty in terms of optimal patient and disease characteristics, the timing of ECT application, and the best combination/sequential approach with other local/locoregional therapies. Additionally, the changing landscape of systemic treatment has opened new clinical scenarios, creating diverse opportunities for a variety of multimodal strategies.

Procedural aspects represent a second controversial area. The ESOPE guidelines were first released in 2006[22] and updated in 2018[23]. By providing the fundamental technical specifications, these guidelines have ensured the reproducibility of results on a broad scale and across malignancies[27]. The use of ECT in melanoma, however, poses peculiar challenges. This is exemplified by in-transit disease, which has a propensity for heterogeneous presentation, multifocal deposits, and widespread subclinical dissemination. Yet, a significant variation exists in ECT application among centres. An example of discrepancy is the inconsistent application of a safety margin around single tumours or an extensive treatment field. This not only jeopardizes ECT use but also precludes the interpretation of its results; therefore, uniformity in assessing disease burden and reporting treatment delivery should be guaranteed to enable reliable evaluations.

No quality indicators exist in ECT practice. Increasing emphasis on quality assurance has stimulated interest in their adoption across healthcare settings and, more recently, in surgical oncology[35,36]. The introduction of ECT-dedicated quality indicators may represent a valuable opportunity to pursue quality assurance programmes in line with NICE guidance[32].

Given the absence of a solid evidence basis, this study aimed to gather the opinion of an international expert panel to explore

these controversial areas, and used the Delphi process as a consensus-seeking approach to develop criteria for the appropriateness of treatment[37–40]. Melanoma experts were engaged by using an online Delphi (e-Delphi) process to solicit their opinions and generate a consensus on ECT treatment indications, procedural aspects, and quality indicators.

Methods

Study design

This was a three-round hybrid Delphi survey (*Fig. S1*) following standard procedures[37,41–43]. After each round, five facilitators (four authors, two of whom were members of the expert panel, and an external collaborator) analysed responses and provided controlled feedback, including pooled results, critical comments, and an updated survey version.

Survey

A review of the pertinent literature generated provisional statements on controversial topics. In the treatment indications domain, the survey included detailed clinical scenarios, including features of skin metastases, disease stage and molecular characteristics, and available treatments (*Fig. S2*). Candidate statements were reviewed at the annual InspECT meeting, and labelled with an identification code to enable tracking and ranking. Then, three external non-health professionals assessed items for clarity, and three authors reviewed the final content. Care was paid to frame statements in a way that would allow for different opinions. Finally, the facilitators and six external health professionals (medicine, 2; psychology, 2; nursing, 2) pilot-tested the online survey, and provided comments on webpage navigation and process flow.

Panel selection

Eligibility criteria were: at least 20 per cent of biomedical practice in melanoma; a minimum of 5 years of postqualification experience; regular participation in the local skin cancer multidisciplinary team meeting; ability to communicate in English; and availability of ECT at own/referral centre. An e-mail was sent to 160 potential participants at 53 European institutions asking for the invitation to be extended to other colleagues. Responders received an e-mail with details of the study and the commitment required. Non-responders received two additional invitations over 6 weeks.

Delphi process

The descriptive parameters are provided in *Table S1*, according to Day *et al.*[44] and Trevelyan *et al.*[45]. A maximum of three rounds interspersed with controlled feedback was adopted to allow participants to reassess their judgments. In the first round, the panellists evaluated each item for relevance, agreement, and clarity. Relevance and agreement were rated on a five-point Likert scale ranging from 1 (lowest relevance/complete disagreement) to 5 (highly relevant/maximum agreement). The clarity of language was categorized as yes/no, and an open-ended field was provided for rephrasing or proposing new statements. The newly entered items were assessed by the same modality. The hands-on experience of panellists with ECT was assessed by asking them to confirm their acquaintance with the procedure. The items were retained in the survey until they reached consensus (stable agreement/disagreement in two consecutive iterations), and the others were reissued. A real-time Delphi method optimized for user-friendliness, data output, and administration[46,47] was applied to determine quality indicator benchmarks in the third round. Participants' anonymity was maintained throughout the study.

Online platform

A dedicated survey tool was developed by Openview (Albignasego, Padua, Italy), an agency specialized in healthcare and medical research surveys. Questionnaires were administered through an online platform (powered by Scientific Network, https://www.scientificnetwork.org), which included state-of-the-art security measures (encryption of passwords, intrusion detection systems, firewall restrictions, and daily hacker safe scans) to protect participants' privacy and confidentiality.

Survey distribution

The panellists were given 8 weeks to complete each round. Automatic early reminders were set up in line with the methodology[48,49]. Questionnaire completion was mandatory to be admitted to the expert panel and participate in the subsequent survey rounds.

Analysis

For each item of the survey, the analysis entailed describing score distribution on the five-point Likert scale, generating pie and bar graphs to provide feedback, and calculating the mean, median, and interquartile range (i.q.r.) values. To be relevant or in agreement, each item had to achieve a mean and a median of at least 3.75, with an i.q.r. of no more than 1.5. The stability of the agreement was defined as the consistency of responses across two successive iterations, and was determined by satisfaction of at least four of the criteria: a stable median within the same category (agreement, 3.75–5; disagreement, 1–2.75); a stable or decreased i.q.r; a non-significant χ^2 (or Fisher's exact) test; a non-significant Wilcoxon signed-rank test; or a significant Spearman's rank correlation test. Statistical analyses were performed using GraphPad Prism® version 8.2.0 for Windows® (GraphPad Software, La Jolla, CA, USA).

Conclusion meeting

Following the third round, five panellists attended a face-to-face meeting to review the results and draft the final list of statements.

Results

Survey

The initial version included 113 items, divided into three domains: treatment indications, 90; procedural aspects, 3; and quality indicators, 20.

Expert panel

Following the invitation, 122 of 160 experts (76 per cent) agreed to participate and accessed the platform. Of these, 18 (15 per cent) did not launch the survey, and four (3 per cent) did not complete it. As a result, the expert panel was composed of 100 members (*Table S2* and *Fig. S3*).

First round

The response rate was 82 per cent (100 of 122) and produced the following list: treatment indications, 50 items (23 of 50 with agreement); procedural aspects, three items (1 of 3 with agreement); quality indicators, 22 items (15 of 22 with agreement).

Table 1 Consensus statement: treatment indications

Item	Consensus statement
1. Burden of skin metastases	
1.1	Skin metastases represent a significant burden for patients, and a therapeutic challenge for nurses and physicians
1.2	ECT reduces the morbidity of skin metastases
1.3	Skin metastases are more symptomatic when located in the scalp, face, neck, hands/feet, axilla/groin
1.4	Painful skin metastases represent an indication for ECT*
2. General considerations on ECT	
2.1	ECT is a cost-effective treatment
2.2	ECT should be performed at referral centres, and indication agreed on within MDT
3. ECT indication according to melanoma stage	
3.1	ECT is an effective treatment in well selected patients with stage IIIB–IIIC disease
3.2	ECT can be combined with other LRT in stage IIIB–IIIC disease
3.3	ECT is an effective treatment in well selected patients with stage IV–M1a disease
3.4	ECT is an effective treatment in well-selected patients with stage IV–M1b/M1c disease (and skin metastases)
3.5	ECT can be applied as a first-line treatment in well selected patients
3.6	ECT can be applied as a first-line treatment in well selected patients with stage IIIB–IIIC disease
4. ECT indication according to the characteristics of skin metastases	
4.1	The number, size, and spread of skin metastases inform patient selection
4.2	In patients with in-transit disease, the most favourable scenarios for considering first-line ECT are the following: • < 10 metastases and maximum tumour size of 1–3 cm • < 20 metastases and maximum tumour size < 1 cm
4.3	Tumour size is a relevant parameter in patient selection for ECT
4.4	The maximum tumour size for optimal ECT treatment is between 1 and 3 cm
4.5	Tumour spread is a relevant parameter in patient selection
4.6	In patients with in-transit disease, ideal superficial tumour spread should be defined as follows: • single limb segment involvement (arm/forearm, thigh/leg) • maximum distance between skin metastases 10 cm
4.7	The number of skin metastases is a relevant parameter in patient selection for ECT
4.8	When considered alone, the ideal maximum number of skin metastases is 10
4.9	The optimal timing of ECT application is: • early—when skin metastases are small (indicatively < 0.5 cm) • when skin metastases become symptomatic (for example ulceration, bleeding)
5. ECT indication according to mutational status and disease stage	
5.1 Mutant *BRAF*	
5.1.1	Stage IIIB–IIIC: • ECT alone as first-line therapy (agreement without consensus)† • ECT plus other LRTs • ECT plus ST
5.1.2	Stage IV–M1a: • ECT in association with ST
5.1.3	Stage IV–M1b/M1c: • ECT in association with ST • ECT only for palliation
5.1.4	Stage IIIB–IIIC—the optimal combination of ECT and ST is: • ST followed by ECT to improve the response (agreement without consensus)† • ST (ECT only in progressing or relapsing disease)
5.1.5	Stage IV–M1a—the optimal combination of ECT and systemic treatment is: • ST followed by ECT (to improve response) • ST (ECT only in progressing or relapsing disease)
5.1.6	Stage IV–M1b/M1c—the optimal combination of ECT and ST is: • ST (ECT only in non-responding disease)
5.2 Wild-type *BRAF*	
5.2.1	Stage IIIB/IIIC: • ECT alone as first-line treatment (agreement without consensus)† • ECT plus other LRTs • ECT plus ST
5.2.2	Stage IV–M1a: • ECT in association with ST
5.2.3	Stage IV–M1b/M1c: • ECT in association with ST • ECT only for palliation
5.2.4	Stage IV–M1a—the optimal combination of ECT and ST is:

(continued)

Table 1 (continued)

Item	Consensus statement
	• ST followed by ECT (to improve response) • ST (ECT only in progressing or relapsing disease)
5.2.5	Stage IV–M1b/M1c—the optimal combination of ECT and ST is: • ST followed by ECT (to improve response) • ST (ECT only in progressing or relapsing disease)
6. Anaesthetic evaluation	
6.1	The following criteria contraindicate ECT application: • performance status (ECOG ≥ 3) • anaesthetic issues • tumour characteristics (number, size, spread)
6.2	The following criteria do not necessarily preclude ECT application: • patient age • failure of previous therapies
6.3	Mildly reduced renal function (GFR 60–89 ml/min/1.73 m^2) should not be an exclusion criterion, provided that bleomycin is de-escalated
7. Treatment toxicity	
7.1	ECT side-effects are more relevant in the following anatomical locations: scalp, face, neck, axilla/groin
7.2	ECT-induced skin toxicity is reversible

*Provided that pain control is optimized before operation. †The statements without consensus are presented for completeness. ECT, electrochemotherapy; MDT, multidisciplinary team; LRT, locoregional therapy; ST, systemic treatment; ECOG, Eastern Cooperative Oncology Group; GFR, glomerular filtration rate.

Second round

The response rate was 97 per cent (97 of 100 panellists) and led to the following list: treatment indications, 48 items (19 with consensus and 29 with no agreement/consensus); procedural aspects, 3 items (one with consensus, and two with no agreement/consensus); and quality indicators, 16 items (14 with consensus, and two with no agreement/consensus).

Third round

The response rate was 93 per cent (90 of 97 panellists), and produced 56 items: treatment indications, 39; procedural aspects, 1; quality indicators, 16 with benchmarks.

Consensus statement

Following the concluding meeting, the reviewed list of statements included 54 items: treatment indications, 37; procedural aspects, 1; and quality indicators, 16.

Treatment indications

A consensus was reached on the following subdomains: burden of skin metastases; general considerations on ECT; treatment indication according to disease stage; treatment indication according to characteristics of skin metastases; treatment indication according to melanoma mutational status, disease stage, and other treatments; preoperative anaesthetic evaluation; and treatment-related toxicity (*Table 1* and *Table S3*).

Procedural aspects

Concerning procedural aspects, a consensus was reached on the adoption of treatment safety margins around tumours (*Fig. 1*, *Table 2*, and *Table S4*).

Quality indicators

The 16 items with benchmarks are listed in *Table 3* and *Table S5*.

Items with agreement but no consensus

Ten items reached agreement only in the third round, precluding achievement of consensus (*Table S6*).

Items without agreement

Three items did not reach agreement (*Fig. 2* and *3*, *Table S7*).

Correlations with panellist background

The responses on procedural aspects correlated with panellist background and acquaintance with ECT. Those involved with the procedure supported the adoption of a treatment safety margin more than panellists who referred patients to other specialists (48 of 52 *versus* 27 of 38; $\chi^2 = 5.7$, $P = 0.017$). Similarly, dermatologists and surgeons supported this strategy more than medical oncologists (25 of 28 *versus* 37 of 42 *versus* 8 of 13 respectively; $\chi^2 = 6.1$, $P = 0.047$). Conversely, there was no correlation with panellist InspECT membership ($P = 0.254$) or nationality ($P = 0.628$). Similar results were observed regarding the adoption of a wide treatment field (32 of 52 ECT users *versus* 13 of 38 non-users, $\chi^2 = 5.5$, $P = 0.018$; 28 of 42 surgeons *versus* 13 of 28 dermatologists *versus* 0 of 13 medical oncologists, $\chi^2 = 17.8$, $P < 0.001$). Again, there was no correlation with InspECT membership ($P = 0.396$) and nationality ($P = 0.279$).

Additional considerations from panel

The expert panel acknowledged the intrinsic local effect of ECT and the current literature gaps, including the absence of comparative studies. Additionally, they highlighted the heterogeneous availability of locoregional therapies among centres (for example ECT, ILP, ILI, T-VEC, investigational drugs) and the opportunity to explore these in conjunction. The panel also remarked on the need to streamline the patient pathway to render ECT a procedure with a one-night stay whenever feasible, and maximize its cost-effectiveness regardless of local reimbursement schemes. Finally, it was highlighted how long-term oncological, functional, and aesthetic outcomes should receive greater consideration. However, panellists raised concerns about the burden of data collection.

Discussion

Experts reached a consensus on controversial topics of ECT in melanoma to improve patient selection, treatment delivery and quality of care, and, ultimately, generate clinical guidance.

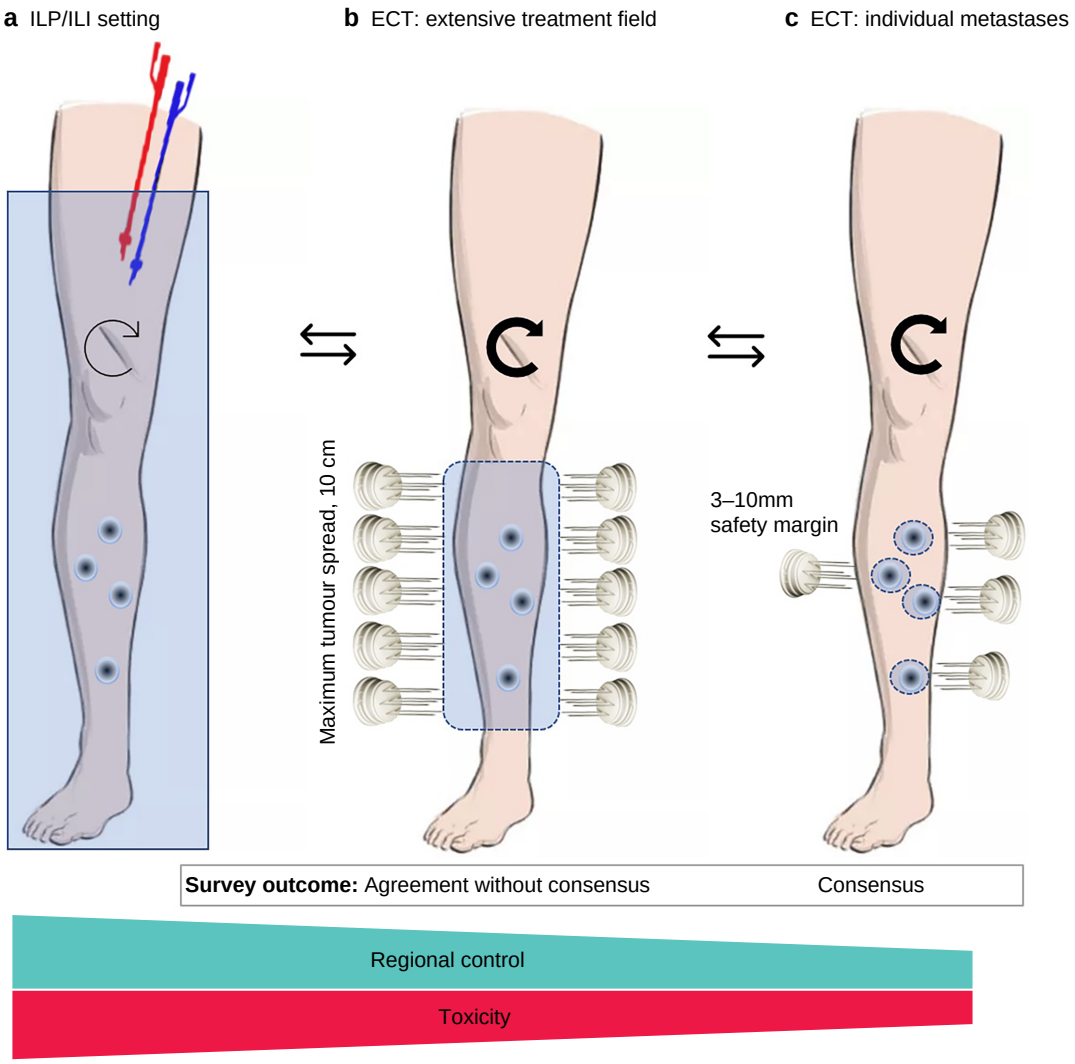

Fig. 1 Procedural aspects of electrochemotherapy compared with locoregional chemotherapy

a Isolated limb perfusion (ILP)/isolated limb infusion (ILI) setting, **b** electrochemotherapy (ECT) with application of an extensive treatment field, and **c** ECT on individual skin metastases, including a safety margin. ECT intent and extension can be modulated according to patient conditions and tumour burden. For example, in patients fit for general anaesthesia and with in-transit disease, ECT may have therapeutic intent; thus, a more aggressive approach could be justified (**b**), including all tumours and the skin between them, similar to ILP/ILI (**a**). Conversely, in frail individuals with metastatic disease, the intent of ECT is often palliative and directed towards control of symptomatic lesions (**c**). The arrows represent possible multimodal combinations: curved arrows indicate the repeatability of the procedure, whereas straight arrows indicate possible sequential combinations of ECT and locoregional chemotherapy.

Table 2 Consensus statement: procedural aspects

Item	Statement	Agreement	Consensus
1. Treatment safety margin			
1.1	It is advisable to include a treatment safety margin around tumours (consensus statement)	+	+
1.2	The extent of the treatment safety margin should be 3–10 mm (provisional statement)	+	–
2. Treatment field			
2.1	It is advisable to include the skin among tumours within the treatment field (provisional statement)	–*	–
2.2	The maximum distance between tumours to justify inclusion of the skin between them in the treatment field is 10 cm (provisional statement)	+†	–

*In the third round, the distribution of panellist responses was: complete disagreement, 1.1 per cent; disagreement, 13.3 per cent; uncertain, 35.6 per cent; agreement, 47.8 per cent; complete agreement, 2.2 per cent (mean score 3.37; median score 3.5). †Detailed panel feedback for this item in the third round: < 2 cm, no agreement (mean score 3.45; median score 4.0); 2–5 cm, no agreement (mean score 3.23; median score 3.0); 5–10 cm, no agreement (mean score 2.91; median score 3.0); 10–20 cm, agreement to reject (mean score 2.43; median score 2.0); > 20 cm, agreement to reject (mean score 2.19; median score 2.0).

Notably, the online process elicited opinions from a diverse panel and yielded consistently low attrition rates. Unfortunately, the current multicontextual nature of healthcare does not facilitate the standardization of surgical care[1]. For example, in melanoma, the advent of novel systemic and injectable therapies unveils unprecedented scenarios and therapeutic

Table 3 Consensus statement: quality indicators

Item	Quality indicator	Goal	Benchmark (% of patients)*
1. Patient selection			
1.1†	Receiving preoperative anaesthetic assessment and pain treatment plan	To reduce complications	100
1.2	Died from disease within the first 3 months (after ECT)	To avoid treatment futility	10
1.3	Lost to follow-up at 6 months (after ECT)	To avoid futility/gather long-term outcomes	15
2. Organizational performance			
2.1	Maximum time on waiting list (weeks)	To improve treatment availability	4
2.2	Assessed with QoL questionnaire (before/after ECT)	To assess QoL outcomes	60
2.3	Uploaded into InspECT register	To standardize data collection	70
2.4	Scheduled as day-surgery/day-hospital procedures	To promote fast patient recovery	80
2.5	With informative procedural reports on tumour burden	To promote comparisons among centres	90
2.6	With informative procedural reports on ECT parameters (drug, electrode, safety margin, extension of treatment field, total number of pulses, tumour coverage, duration)	To evaluate the effectiveness of different treatment modalities	95
3. Patient outcome			
3.1	Experiencing severe pain at end of procedure‡	To reduce immediate post-treatment pain	< 10
3.2	Experiencing in-hospital adverse events (any category‡)	To reduce side-effects	50
3.3	Percentage of patients with severe pain 1 month after ECT‡	To reduce post-treatment pain	< 10
3.4	Reporting skin infection within 1 month after ECT‡	To reduce skin toxicity	10
3.5§	Readmitted within 1 month after ECT	To reduce treatment side-effects	5
3.6	Experiencing treatment-induced skin ulceration at 2 months‡	To reduce skin toxicity	< 15
3.7	Accepting retreatment (assessed at 1 and 2 months)	To evaluate patient-reported outcomes	80

*Best possible outcome that can be achieved under optimal conditions. †This item was introduced in the third round, wherein 81.1 per cent of the panellists expressed moderate–complete agreement with its adoption (mean score 3.94; median score 4; i.q.r. 0), thus qualifying for agreement without consensus. ‡According to the Common Toxicity Criteria for Adverse Events version 5.0. §This item reached formal agreement only in the third round (mean score 3.90; median score 4; i.q.r. 0), thus qualifying for agreement without consensus. ECT, electrochemotherapy; QoL, quality of life.

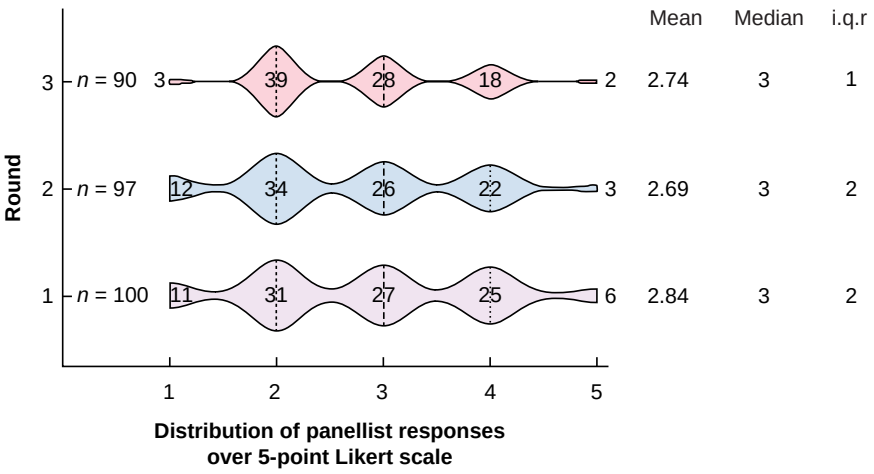

Fig. 2 Item without agreement: a skin-directed treament such as electrochemotherapy should be considered in every patient at the first occurrence of skin metastases

Violin plot showing the distribution of panellists' opinions on the combination/sequencing approaches of electrochemotherapy and locoregional chemotherapies. Responses were registered on a five-point Likert scale: 1, strongly disagree; 2, disagree; 3, undecided; 4, agree; 5, strongly agree.

opportunities[50]. To address the complexity of this novel landscape, objective selection criteria, standardization, and audit are crucial. So far, this is an unmet need in ECT practice because of the lack of data supporting patient selection (except for the inverse correlation between tumour size and response), treatment of application, and outcome assessment.

Till now, only predictors of response have been identified, such as the absence of visceral metastases, absence of previous irradiation, small tumour size, and coverage of tumour margins[24]. There are several important updates from this consensus (*Table 1*). Skin metastases were unanimously deemed a significant burden, primarily in sensitive regions, and ECT an effective option for reducing their morbidity, provided that early optimization of pain control is ensured[51]. Moreover, despite the scarcity of comparative economic analyses, the panel considered the procedure cost-effective[52,53]. Undoubtedly, ECT

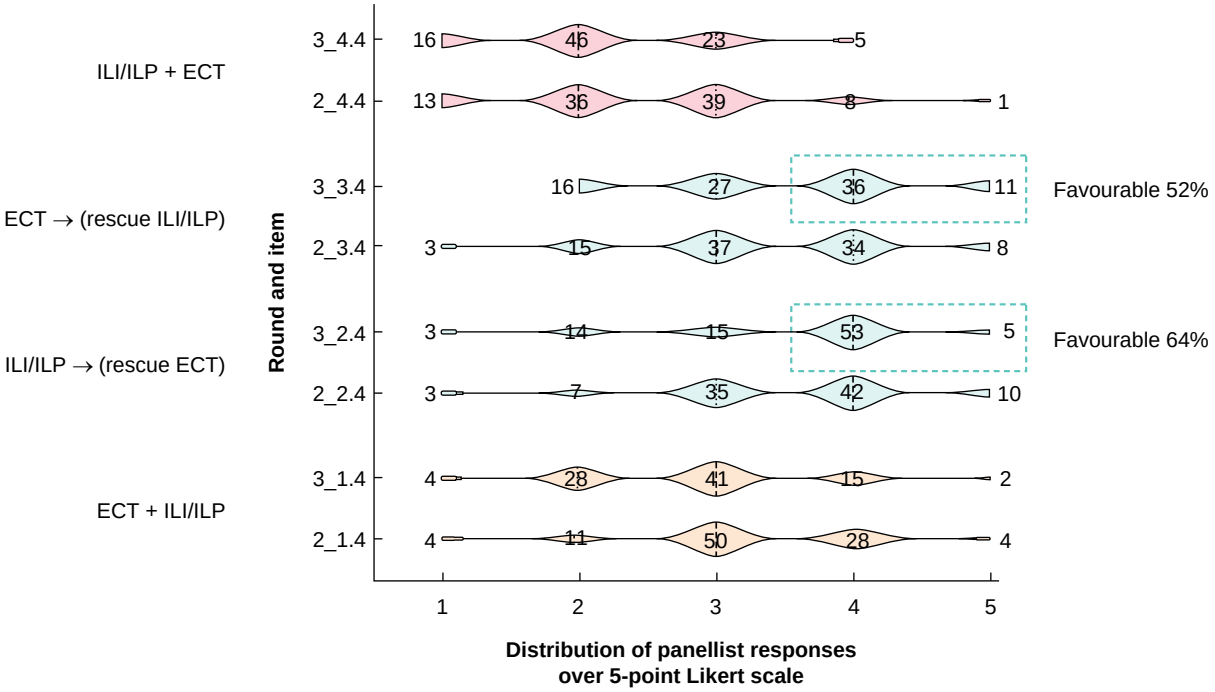

Fig. 3 Items without agreement: in patients with in-transit limb melanoma, which is the optimal combination/sequence of electrochemotherapy and isolated limb perfusion/isolated limb infusion (or other locoregional treatments)?

Violin plot showing the distribution of panellists' opinions on the optimal timing of application of electrochemotherapy (ECT) or other skin-directed therapies. Responses were registered on a five-point Likert scale: 1, strongly disagree; 2, disagree; 3, undecided; 4, agree; 5, strongly agree. ILI, isolated limb infusion; ILP, isolated limb perfusion.

compares well with other regional therapies such as radiation or tumour necrosis factor-based ILP. Head-to-head comparisons have not been conducted, however, and outcomes are difficult to assess owing to the intrinsic differences between techniques (*Fig. 1*)[27,54,55]. Notably, the panel recommended that ECT be performed at referral centres and agreed within a multidisciplinary group, in line with the NICE recommendations[32]. Appropriate referral allows patients to benefit from the broadest range of therapeutic options, including participation in clinical trials. ECT was finally judged as an effective palliative option across melanoma stages and, potentially, an upfront treatment in well selected patients with stage III disease who are unfit for more invasive procedures or systemic treatment.

Regarding feasibility, assessment of the number, size, and spread of skin metastases is mandatory. As general guiding criteria, the ideal candidate should have fewer than 10 tumours smaller than 3 cm, or fewer than 20 smaller than 1 cm. Additionally, they should involve the same limb segment over an area not exceeding 10 cm. Concerning timing, the panellists agreed in principle on either early or late application (*Table 1*); nonetheless, when challenged further, they grappled with upfront ECT (*Fig. 3*) and seemed to prefer its combination with systemic treatment (*Table S7*). Interestingly, they advocated a combined approach in stage IV–M1a and III disease, likely supported by recent evidence for the efficacy of checkpoint inhibitors and, to a lesser extent, targeted therapies in locoregional melanoma[13,56]. Of note, the approval of adjuvant pembrolizumab for stage II melanoma[57] might restrict eligibility for immunotherapy in patients whose disease recurs, thus reducing the available combined strategies with local therapies.

In the preoperative work-up, performance status, anaesthetic concerns, and characteristics of skin metastases emerged as potential deterrents, contrary to patient age, failure of previous therapies, and mild impairment of renal function. In this regard, it should be noted that ECT, unlike ILP or ILI, can be applied safely under local or locoregional anaesthesia, also depending on disease burden and distribution. Therefore, despite a consensus on anaesthetic issues as a contraindication (*Table 1*, item 6.1), less invasive anaesthetic strategies represent a valuable option in well selected patients for ECT[26]. The panellists finally acknowledged the reversibility of ECT side-effects; however, the scalp, face, neck, and axillary/inguinal folds remain critical sites.

The expert panel agreed on applying a treatment safety margin, although its extent remained controversial as it was suggested to be between 3 and 10 mm. Nonetheless, this seems feasible and safe for most patients from a clinical standpoint. Conversely, the adoption of an extensive ECT field, including the macroscopically tumour-free skin in between metastases, remained controversial despite having the support of 50 per cent of the panellists, mainly the ECT users. About half of patients with melanoma need repeated treatment following a partial response or occurrence of new lesions[30]. Therefore, wider coverage may avert this risk and influence local control to a large extent. Prospective studies are needed to assess the efficacy and safety of such an approach. To this aim, panellists were asked to indicate the maximum acceptable tumour spread, and, although this is a provisional statement, a 10-cm ECT field provided the best risk–benefit trade-off (*Fig. 1*).

The quality indicators cover the three dimensions of care (structure, process, and outcome) according to the Donabedian paradigm[58]. The panellists first remarked on the importance of appropriate selection criteria, and proposed the percentage of patients receiving a preoperative anaesthetic evaluation, who die within the first 3 months, and lost to follow-up as a measure

of treatment futility. Interestingly, recent research has suggested that baseline QoL may also inform patient selection[31]. The expert panel also emphasized time on the waiting list, QoL assessment, use of an international register, the proportion of 1-day/day-hospital procedures and completeness of reporting. They finally proposed quality indicators exploring morbidity and patient perception. Despite having a safe profile, ECT carries a risk of pain in up to 36–39 per cent of patients[24,59,60] and skin ulceration in 18–26 per cent[29,61,62]; hence a constant need for assessing patient perspective. As a collateral observation, the panel advocated extended follow-up (more than 2 months) in future studies. The proposed benchmark figures set standards and may help clinicians monitor their practice. For example, they can be adopted in local audits to identify critical aspects and promote change in line with NICE recommendations[32], similar to the quality control programme of the European Organisation for Research and Treatment of Cancer (EORTC) Melanoma Group for ILP[63]. Quality assurance is critical to achieving consistency among centres and standardizing patient care. Further collaborative work towards agreed and validated quality indicators will be the next step.

The residual controversial items bring to light important research questions. Ten items (treatment indications, 8; procedural aspects, 2) reached agreement in the last round (*Table S6*). ECT could be a rescue option in patients with stage III disease following other locoregional therapies, and consolidate response in those with stage IV disease on systemic treatment. This view supports the positive results of ECT in early clinical experiences[64,65]. Identification of optimal schedules and prospective studies are, however, first necessary. Interestingly, ECT was felt as a potential frontline option in well selected patients with stage IV–M1a disease, with a low disease burden and prevalent co-morbidities. Recent data also support the safety of ECT in extreme age groups[66]. The panel advocated lung imaging to prevent bleomycin toxicity, and welcomed the inclusion of patients with moderate renal functional impairment. These can be managed safely with a kidney specialist, de-escalated doses[67,68], intratumoral injection[22,23], or, although investigational, calcium electroporation[69]. The panel finally concurred on a 3–10-mm treatment safety margin and a 10-cm ECT field. Whether to target single tumours or to apply an extensive field needs further investigation. Although supported by most panellists, three items did not reach an agreement (*Table S7*). In patients with low-burden in-transit disease, the sequential administration of ILP/ILI and ECT (or vice versa) was preferred over their concurrent application (*Fig. 3*). Here, the guiding criteria should be patient fitness and personal preferences, with ILP/ILI ensuring homogeneous drug exposure, and ECT a safe and less invasive alternative (*Fig. 1*). Uncertainty also persisted regarding ECT timing (*Fig. 2*). Notably, 60 per cent of respondents advocated its investigation with systemic treatment based on compelling evidence from cohort analyses. Two multicentre studies[70,71] confirmed the feasibility of ECT in combination with checkpoint inhibitors (mainly ipilimumab) with no new safety signals. An ongoing phase II study of the pembrolizumab–ECT combination will evaluate improvement in response and immune correlates (ClinicalTrials.gov: NCT03448666). More recently, a joint retrospective analysis of the InspECT and Slovenian cancer registries[72] indicated improved survival outcomes after ECT and pembrolizumab. Finally, the uncertainty regarding *BRAF* mutation status as a selection criterion was not surprising. Synergistic vemurafenib–ECT interaction was shown only in *BRAF*-mutated cell lines[73]. Nevertheless, in patients receiving targeted therapy, ECT may be effective against resistant clones[64], whereas the release of tumour antigens in patients on checkpoint inhibitors may stimulate the immune system and improve systemic response[70–72,74,75]. Despite sporadic reports on the abscopal effect, systemic immune activation following ECT has not been documented[76].

The consensus statements are susceptible to review based on emerging evidence. As the melanoma therapeutic environment has become fluid, the therapeutic strategy requires coordination from the healthcare team, including patient engagement and patient-reported outcomes[1,77,78]. Additionally, given the selective nature of the survey, unanswered questions remain. For example, a Delphi process on the treatment of in-transit melanoma promoted by multidisciplinary collaboratives such as the EORTC Melanoma Group[36,79] could be envisioned as the next step towards gaining insight into this field. Uncontrolled skin metastases are associated with a physical and psychological burden[6], and the economic impact of disability, family support, and resource use is substantial. Pending the publication of novel data, timely expert opinion and consensus advice is crucial to inform clinical practice.

The main strengths of this study are its rigorous methodology, anonymous and democratic participation, and the large size and multidisciplinary composition of the expert panel. Remarkably, it relied on an inclusive group, not limited to ECT experts, which was nonetheless defined by the adoption of strict inclusion criteria to ensure the reliability of responses[80]. The web-based environment ensured low attrition rates, high-quality data, and reduced survey turnaround. Conversely, the results of this study need to be interpreted with caution. In the Delphi process, the intensity of communication among participants is lower than with other consensus-seeking methods. The expert panel was mainly drawn from Italian centres, potentially reducing the generalizability of the results. Additionally, two of the authors acted as both panellists and facilitators, raising the possibility of subjective interpretation and influence on feedback. Despite careful preparation, it cannot be excluded that ambiguous instructions may have introduced misinterpretations, distortions or systematic biases[81]. An expert consensus does not always provide the answer to clinical questions, and cannot promote any treatment to the standard of care without an adequate evidence base[82]. As such, it does not replace high-quality reporting[83] and rigorous evaluation of original research[27,34,84].

In this study, an expert panel produced a list of consensus statements on ECT treatment indications, procedural aspects, and quality indicators, which provide reliable advice with broad clinical implications. These can be used to harmonize practices between centres, enable quality assurance programmes, and propel high-quality international collaboration. The persisting controversial topics may inspire investigators in the design of future research and clinical studies.

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Supplementary material

Supplementary material is available at *BJS* online.

Data availability

The research data are available from the corresponding author upon reasonable request.

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