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Health-related quality of life trajectories in melanoma patients after electrochemotherapy: real-world insights from the InspECT register

Keywords: Melanoma; Quality of Life; Electrochemotherapy; Palliative Care; Patient Reported Outcome Measures; Dermatologic Surgical Procedures

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Conflicts of interest

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Data availability

The data supporting this study's findings are available from the corresponding author upon reasonable request.

Background Electrochemotherapy (ECT) effectively controls skin metastases from cutaneous melanoma.

Objectives This study aimed to evaluate health-related quality of life (HRQoL) in melanoma patients pre-/post-ECT and its effect on treatment outcome.

Methods The analysis included prospective data from the International Network for Sharing Practices of ECT register. Following the Standard Operating Procedures, patients received intravenous or intratumoural bleomycin (15,000 IU/m^2; 1000 IU mL/cm^3) followed by 100-microsecond, 1000-V/cm electric pulses. Endpoints included response (RECIST v3.0), local progression-free survival (LPFS), toxicity (CTCAE v5.0), and patient-reported HRQoL at baseline, one, two, four and ten months (EuroQol [EQ-5D-3L], including 5-item utility score [EQ-5D] and visual analogue scale for self-reported health state [EQ-VAS]). Comparisons within/between subgroups were made for statistical and minimal important differences (MID). HRQoL scores and clinical covariates were analysed to identify predictors of response in multivariate analysis.

Results Median tumour size was 2 cm. Complete response rate, G3 toxicity and one-year LPFS in 378 patients (76% of the melanoma cohort) were 47%, 5%, and 78%. At baseline, age-paired HRQoL did not differ from the general European population. Following ECT, both EQ-5D and EQ-VAS scores remained within MID boundaries, particularly among complete responders. A

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subanalysis of the EQ-5D items revealed a statistically significant deterioration in pain/discomfort and mobility (restored within four months), and self-care and usual activities (throughout the follow-up) domains. Concomitant checkpoint inhibition correlated with better EQ-5D and EQ-VAS trajectories. Baseline EQ-5D was the exclusive independent predictor for complete response (RR 14.76, p=0.001).

Conclusions: HRQoL of ECT melanoma patients parallels the general population and is preserved in complete responders. Transient deterioration in pain/discomfort and mobility and persistent decline in self-care and usual activities may warrant targeted support interventions. Combination with checkpoint inhibitors is associated with better QoL outcomes. Baseline HRQoL provides predictive information which can help identify patients most likely to respond.

Introduction

An increasing body of literature indicates that electrochemotherapy (ECT) is safe and well-tolerated in patients with inoperable skin cancers or cutaneous metastases unresponsive to conventional therapies.[1,2] In patients with superficially metastatic melanoma, it provides durable local control with no toxicity concerns, alone or with systemic treatment.[3–5] Nonetheless, recent meta-analyses, despite confirming the efficacy, critically highlight the lack of patient-reported outcomes (PROs) quality of life (QoL) data.[6,7]. Even in the era of anti-BRAF therapies and checkpoint inhibitors, this information is all the more essential for a palliative intervention such as ECT, whose priority is QoL preservation. Skin metastases remain a challenging issue, often associated with debilitating symptoms affecting the physical, emotional, and social sphere, depending upon their anatomical location and distribution.[8–10] Additionally, the heterogeneity of their clinical presentation is reflected in a broad spectrum of associated symptoms (e.g. itching, pain, bleeding, infection, exudation, odour). These symptoms, and the associated functional limitations, result in varying degrees of depression, fear, and anxiety.[8] Locoregional therapies are essential in disease control and QoL preservation in melanoma patients.[9,10] Among them, ECT combines low-toxic chemotherapy and brief electric pulses to achieve transient tumour permeabilisation (reversible electroporation) and effective drug delivery.[11] Symptomatic benefits include reduced pain, improved wound healing and bleeding control and overall health perception.[12,13] These favourable effects, coupled with the low incidence of treatment-related

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toxicity, explain the high acceptance of retreatment reported in various series.[13,14] The objective of this study is to evaluate the health-related QoL (HRQoL) of melanoma patients pre- and post-ECT.

Materials and methods

This was an observational study. The population of interest consisted of 378 melanoma patients with skin metastases prospectively included in the International Network for Sharing Practices of ECT (InspECT) register (http://www.insp-ect.org). Patients were treated at 27 InspECT centres in seven European Countries (**Table 1**). The research was approved by local Ethics Committees and conducted according to the rules of Good Clinical Practice (Declaration of Helsinki). Treatment indications were based on institutional clinical pathways and agreed upon multidisciplinary discussion. The accrual ranged from January 2010 to January 2021.

Procedure

ECT was delivered using the European Standard Operating Procedures of Electrochemotherapy (ESOPE).[15,16] Anaesthesia regimen, pain management schedule, and wound dressing were according to local protocols. In all cases, the chemotherapy drug was bleomycin administered either intratumourally (at a dose of 1000 IU mL/cm^3 of tumour tissue) or intravenously (at 15 000 IU/m^2 of body surface area). One of the following electrode geometries was used as a pulse applicator depending on tumour characteristics: plate (contact), row or hexagonal needle.[17] Electric fields (eight pulses of 100 µs duration and 5 kHz repetition frequency) were delivered using a square wave pulse generator (Cliniporator™, IGEA, Carpi, Italy).

Outcome assessment

Collected data included baseline patient and tumour characteristics, ECT procedural details, toxicity (graded according to the Common Toxicity Criteria for Adverse Events [CTCAE v5.0]), local tumour response two months after ECT (Response Evaluation Criteria In Solid Tumours [RECIST v1.0][18]), local progression-free survival (LPFS), overall survival (OS), and HRQoL (assessed using the EuroQoL questionnaire [EQ-5D-3L, self-complete version on paper[19]]). A maximum of seven

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cutaneous metastases (including the largest) were registered as target lesions for response assessment.

The EQ-5D-3L includes a descriptive system based on five items (exploring the domains of pain/discomfort, mobility, usual activities, social relations, depression/anxiety) pooled into the EQ-5D utility score and a patient-reported visual analogue scale (EQ-VAS) for overall health ranging from 0 (worst state) to 100 (best state). Each of the five dimensions of the descriptive system is graded into three levels (1 = no problem, 2 = some/moderate problems, 3 = severe problems). Assessments were carried out at baseline and one, two, four and ten months following ECT. The mean absolute EQ-5D utility score and EQ-VAS score at baseline and each follow-up were calculated along with the mean differences from the baseline. These differences were compared with the minimally important differences (MID) identified by Pickard AS et al.[20] Since the numbers of assessments differed from patient to patient (median 3, range 1-5), we introduced a summary of the EQ-5D-3L data utilising the area under the curve (AUC).[21] Accordingly, the EQ-5D and EQ-VAS over time were collapsed into AUC summary statistics for each patient.

Statistical analysis

Values are reported as mean and standard deviation or median and range, whereas categorical variables as absolute counts with percentages. Comparisons between groups were performed by Kolmogorov-Smirnov test and comparison between repeated evaluations within the same group by paired Wilcoxon test for non-parametric variables. When evaluating within-group EQ-5D and EQ-VAS differences, besides the paired test for statistical significance of differences, we used the Minimal Important Difference (MID) cut-offs as defined by Pickard et al.[20] LPFS indicated the interval from ECT to recurrence/progression within the ECT field. The Kaplan–Meier method was used to estimate the LPFS curve. All statistical analyses were performed using NCSS 9 [NCSS 9 Statistical Software (2013). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/ncss].

Results

1. *Patient characteristics*

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Patient characteristics (n=378, 76% of the entire InspECT melanoma cohort with available QoL information) are listed in **Table 1**.

2. Baseline HRQoL

The EQ-5D score was similar among InspECT countries, whereas the EQ-VAS showed significant differences, with the highest and lowest values in the Italian (n=113 patients) and German (n=43 patients) cohorts (73.98 and 60.91, respectively, p=0.001; **Suppl. Table 1**).

Next, baseline InspECT cohort scores were plotted according to patient age and compared with the general population of the corresponding European countries.[22] The EQ-5D and EQ-VAS scores showed a progressive decline with the increasing age in all groups (**Figure 1**). Notably, the InspECT scores remained within the distribution of the general population, with tendentially lower values in the 25-54 years age group and higher values in the 65+ age group. Finally, baseline QoL scores were comparable with other major series of metastatic melanoma (**Suppl. Table 2**).

3. Baseline HRQoL according to disease characteristics

HRQoL was assessed according to tumour features. Tumour size was associated with a significant decrease of either EQ-5D (0.765±0.222 vs 0.691±207, p=0.003) and EQ-VAS (72±19 vs 67±18 in patients with ≥3 and <3 cm tumours, respectively, p=0.049). Similarly, ulceration significantly correlated with either EQ-5D (0.773±0.210 vs 0.655±0.224 p<0.001) and EQ-VAS (72±18 vs 64±19 in patients with non-ulcerated and ulcerated tumours, respectively, p=0.002). Conversely, neither the number of skin metastases (EQ-5D, p=0.518; EQ-VAS, p=0.560) nor their anatomical location (EQ-5D, p=0.527; EQ-VAS, p=0.353) correlated with PROs.

4. Tumour response to ECT and local control

After a single course of treatment, the overall response rate (ORR) was 80%, with 47% of patients achieving a complete response (CR). Stable disease (SD) was observed in 13%, and 5% developed progressive disease (PD); the response was not evaluable in 2% of cases. Forty-nine individuals (13%) underwent retreatment. One-, 2- and 3-year local tumour control rate was 78% (C.I. 71%-85%), 68% (C.I. 58%-77%) and 62% (C.I. 50%-74%) (**Suppl. Fig. 2**).

5. Toxicity

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At baseline, superficial disease-associated symptoms in the 378 patients included ulceration (26%, grade-3 in 8%), hyperpigmentation (19%, grade-2 in 6%), suppuration (15%, grade-3 in 2%), and odour (14%, grade-2 in 4%). Within 30 days from ECT, the side effects observed among 185 patients were ulceration (33%, grade-3 in 5%), hyperpigmentation (27%, grade-2 in 2%), suppuration (18%, grade-3 in 1%), and odour (12%) (**Suppl. Fig. 3**). Systemic side effects were uncommon and included mild flu-like symptoms and nausea. Our results showed no statistically significant difference in toxicity profile according to the use or not of immune checkpoint inhibitors, with the only exception noted at ten months, when body odour scores favoured the immunotherapy subgroup (**Suppl. Table 4**).

6. HRQoL after ECT

In general, we did not observe any pre-/post-ECT clinically meaningful consistent changes. Trajectories of pooled EQ-5D and EQ-VAS scores are presented in **Figure 2**. The EQ-VAS remained stable throughout the follow-up. Conversely, EQ-5D deteriorated at one and, more significantly, two months (p=0.02 and p=0.002, respectively), even though these changes remained within the MID threshold. Next, we sub-analysed the five items of the EQ-5D utility score and found a statistically significant deterioration in the domains of pain/discomfort (at one and two months), mobility (at two months), and usual activities and self-care (at all time points); there was no variation in the anxiety/depression scale (**Figure 3** and **Suppl. Table 3**).

7. Parameters influencing QoL outcome

HRQoL trajectories were analysed according to Eastern Cooperative Oncology Group Performance Status (ECOG-PS) and response to ECT (**Fig. 4**), previous systemic treatment and concomitant immunotherapy (**Fig. 5**), disease stage and toxicity (**Fig. 6**).

7.1 *ECOG PS and response to ECT*

Patients with low ECOG-PS and good response to ECT consistently reported better EQ-5D and EQ-VAS scores than their counterparts, with QoL trajectories always within the MID thresholds. Of note, there was a clinically important deterioration in patients with high ECOG-PS and SD/PD following ECT, with both EQ-5D and EQ-VAS surpassing the MID threshold (**Fig. 4b,d,f**). Importantly, these findings were confirmed when assessing the AUC outcomes (**Table 3**).

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7.2 *Previous systemic treatment and adjuvant immunotherapy*

Patients who received systemic immunotherapy after ECT reported statistically significant higher EQ-5D and EQ-VAS scores than the other patients (**Fig. 5e,g**) and no clinically significant changes compared to baseline (**Fig. 5f,h**). Notably, they tended to have higher and progressively increasing EQ-5D and EQ-VAS scores culminating in a statistically significant difference in the EQ-5D at ten months (**Fig. 5e**).

Patients naïve from previous systemic treatment consistently reported higher EQ-5D and EQ-VAS scores than pre-treated patients, except for a single and clinically significant EQ-5D deterioration at one month (**Fig. 5b**). Subsequently, their EQ-5D score remained lower than the baseline (with statistically significant differences at two and ten months), although within the MID threshold. By contrast, the pre-treated patients did not report any clinically significant variation (**Fig. 5b,d**), with inter-group statistically significant differences observed at baseline and two months (**Fig. 5a,b**).

7.3 Disease stage, route of bleomycin administration and toxicity

We did not observe any intra- or inter-group variation according to disease stage (**Fig. 6a-d**) and bleomycin regimen (**Suppl. Table 5**). Conversely, patients who did not experience ECT-related toxicity reported statistically significant higher EQ-5D and EQ-VAS scores than the other patients (**Fig. 6e,g**), although in the absence of clinically significant variations compared to baseline (**Fig. 6f,h**).

8. Predictors of response

Next, we aimed to determine whether PROs can predict patient outcomes and performed a multivariate analysis for CR to ECT, including QoL variables and conventional clinical covariates. Of note, the EQ-5D score was the sole independent predictive factor (RR 14.76, 95% C.I. 2.81-77.60, p=0.001; **Table 2**).

Discussion

PROs are a critical component of high-quality, patient-centred health care.[23] This study used the EQ-5D questionnaire to explore patient-reported HRQoL in a cohort with locally advanced and

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metastatic melanoma treated with ECT. Providing sound QOL data to melanoma professionals and patients is essential for genuinely informed decision-making when varied treatment strategies exist and no one-size-fits-all approach is available.[9,10] Nowadays, patients demand that QoL be considered a primary outcome of their care, and research is increasingly demonstrating its importance.[24] Thus, in the absence of ECT survival benefits, QoL outcomes are crucial to informing clinical decision-making and patient choices.

Baseline HRQoL

Despite skin metastases often representing a cause of additional interventions, disfigurement and distress,[8] PROs in the InspECT cohort were similar to the general European population, with no clinically or statistically significant differences across all age groups. It can be argued that the patients included in this study received timely treatment, as shown by the limited superficial tumour load (**Table 1**), and perhaps only marginally experienced the impact of skin metastases. Additionally, with increasing clinical confidence in the procedure and evidence indicating favourable outcomes in patients with low-volume disease, clinicians may have adopted restrictive selection criteria.[3,4] Lastly, tumour ulceration and large tumour size, features known to affect QoL,[5] were present only in a minority of patients.

In the InspECT cohort, the EQ-5D score of the younger age group (26-54 years) was closer to the lower limits reported by the healthy population, suggesting a more significant impact of the disease in this subset. This finding should not surprise, given the more detrimental effect of the disease on the active population. Conversely, the EQ-5D scores of the elderly patients fell well within the values of the general population, arguably diluted by the presence of comorbidities (this information is not included in the InspECT register). Additionally, on a more general level, there is evidence that ageing, per se, does not negatively influence QoL with all other influences controlled.[25] Finally, as a collateral observation, there were no differences between the InspECT cohort and major published series of metastatic melanoma assessed with the EQ-5D questionnaire (Suppl. Table 2). Collectively, these findings suggest that patients with metastatic melanoma treated with ECT can preserve their QoL.

HRQoL after ECT

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Overall, we found evidence of HRQoL stability, consistent with the reported efficacy (ORR, 80%) and toxicity (G3, 5%). While there was no variation in the patient-reported overall health, we did observe a statistically, although not clinically significant, decrease in the EQ-5D, which rebounded within four months. Interestingly, although the aggregate score did not surpass the MID threshold, the sub-analysis of its five underpinning items revealed some changes worth discussing. In particular, we observed an early deterioration in pain/discomfort and mobility and persistent deterioration in self-care and usual activities domains. The transient worsening of pain and mobility are likely interconnected. A dedicated InspECT study showed that patient-reported pain (moderate, 13%; severe, 13%) recovered within 45 days after the procedure.[12] On the other hand, the persistent, although below the MID threshold, deterioration in the self-care and usual activities may be multifactorial. Contributing factors include the cutaneous disease itself, post-treatment pain (and its management), eventual dermatologic side-effects, patient age (median, 75 years) and independence status, and the initiation of other oncological treatments or additional ECT sessions (13% of patients).

Parameters influencing QoL trajectories

We conducted an exploratory subgroup analysis to identify potential QoL outcome predictors. Interestingly, high ECOG-PS and unresponsiveness to ECT correlated with a clinically meaningful deterioration. These findings reiterate the importance of patient functional status as a selection criterion and the need for additional early interventions in non-responders.

The impact of post-ECT toxicity on QoL is a relevant issue. The patients who did not experience any side effects reported higher utility scores than the others (**Fig. 6e**). Importantly, since no evidence links more intense toxicity with improved response to ECT (**Table 2**), collectively, our observations reiterate the importance of adopting strategies to reduce the risk of side effects and preserve patient QoL.[26]

Other observations emerged from the analysis of patterns of systemic treatment. First, concerning previous treatment, PROs were stable, except for a drop of the EQ-VAS score at one month in treatment naïve patients. Second, and perhaps more interestingly, we observed no cumulative toxicity and a progressive improvement of the EQ-5D and EQ-VAS scores in patients who received immunotherapy following ECT, with a significant long-term effect (**Fig. 5e**). In this

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regard, checkpoint inhibitors have been found, alone or in combination, to confer a beneficial effect on QoL in large randomised trials.[27,28] Additionally, a recent study from the InspECT and Slovenian Cancer registry suggests a synergistic beneficial effect of ECT and checkpoint inhibition on tumour control and OS,[29] thus confirming previous observations.[30,31] Overall, our findings reinforce the notion of an actual clinical benefit deriving from checkpoint inhibition and locoregional therapies.

Strategies to improve HRQoL

Despite ECT being a low demanding procedure, with most patients carrying on with their activities, pain management should be planned as part of the routine anaesthesiologic assessment.[15,32] Crucially, poorly controlled pain is detrimental also for other QoL domains. Of note, a previous analysis of the InspECT database identified pre-existing pain, tumour size, previous irradiation, and high intraprocedural electric currents as possible predictors for pain.[12] Interestingly, the present analysis raises the question of whether exploring other targeted interventions relevant to the domains of self-care and usual activities. Additional support may include patient empowerment, prehabilitation/rehabilitation programs, intensified management of skin-associated symptoms, help with practical concerns, or tailored assistance to patient family and caregivers.[33]

Predictive value of QoL

Last, but perhaps most interestingly, the baseline EQ-VAS score resulted in the exclusive predictor of CR to treatment, outperforming even tumour size in the multivariate analysis.[3–5] Thus, by providing additional and agile predictive information, patient-reported QoL supplements traditional clinical factors and may allow clinicians to predict patients more likely to respond. At the same time, when interpreting these results, we believe it is essential to consider that the median tumour size in our series was 2 cm; therefore, we can feel confident in proposing baseline QoL as a predictive factor when candidate tumours range to this size.

Baseline overall QoL has been already demonstrated to be prognostic for survival in melanoma patients receiving systemic treatment.[34,35] Our results collectively point to the notion that patients with better QoL at baseline are more likely to achieve CR following ECT (Table 2) and,

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thereof, maintain their QoL (**Fig. 4a,c**). The cancer journey of patients with superficially metastatic melanoma is complex, subject to uncertainty, and characterised by varying QoL impacts. This study supplies clear evidence to establishing PROs as an instrument enabling clinicians to draw on patient experience to predict treatment results and monitor outcomes during follow-up. The rationale for this approach is that it is a prerequisite for ensuring genuinely patient-centred care. Moreover, the principle of incorporating patients' views should not be seen as a one-off activity but rather a continuous cycle to evaluate and improve the quality of ECT services.

Study limitations

There are limitations to this study to be considered. First, the analysis was exploratory; nonetheless, it has generated new intriguing research hypotheses. Second, we used a generic questionnaire. Disease-oriented instruments (e.g. the FACT-M, QLQ-MEL38, Skin Cancer Index) are available to provide more accurate insights in future studies.[36,37]. Notably, the combination of a generic and dermatology-specific tool is recommended as the optimal approach by the European Academy for Dermatology and Venereology (EADV) Taskforce on Quality of Life.[38–40] Third, although the notion of MID helps to interpret differences in QOL scores, a recent EORTC study found that it may not apply to all settings.[41] Fourth, the response rate declined over the follow-up (**Suppl. Fig. 1**), presumably driven by non-responding subjects, thus producing a selection bias. Fifth, we cannot ascribe QoL preservation to ECT without a comparative arm. Nonetheless, the reported activity and toxicity data, coupled with enduring effects on tumour control and PROs, corroborate the beneficial effect of the procedure. Sixth, it is recognised that patients with melanoma or other conditions may provide differing PROs for the same health state, also depending on concomitant factors.[42] Likewise, it should be noted that the patients were treated over an 11-year span, alongside continuous changes in the therapeutic landscape. Finally, on a broader note, the reader should consider that cancer patients receive diverse types of skincare, which may influence their QoL perception (e.g. depending on the availability of advanced wound interventions or specifically designed dermatologic products).[43,44] We acknowledge and welcome the continuous effort to strengthen QoL and PROs research in

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oncology.[45] Nonetheless, despite the above limitations, we believe this study contributes to closing a gap around the palliative value of ECT, in agreement with current recommendations.[46]

Whether and when ECT is preferable to other locoregional therapies is yet to be determined. Similarly, whether the same favourable QoL outcomes are achievable in patients with a higher tumour burden must be investigated. Meanwhile, we show for the first time that ECT can be used in melanoma to control skin metastases and preserve QoL. Discussions between doctors and patients regarding therapeutic decisions are complex and susceptible to a mismatch between expectations and results.[47] Thus, a conjoint analysis of predicted benefits, side effects, and QoL outcomes may enable clinicians to better assess treatment efficacy and inform patient choices.[24,48]

Conclusions

HRQoL of melanoma patients candidates for ECT is similar to the general population and remains stable in the ~50% with CR.

Early deterioration in the pain/discomfort and mobility domain and persistent low self-care and usual activity scores may warrant further investigation and targeted interventions.

The patients who received concomitant checkpoint inhibitors reported a better HRQoL profile.

Baseline QoL is a new powerful predictor of CR to ECT in subjects with intermediate/low tumour burden, even surpassing tumour size in multivariate analysis, which may help clinicians predict results and patients conceive realistic expectations.

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References

1. Clover AJP, Salwa SP, Bourke MG, et al. Electrochemotherapy for the treatment of primary basal cell carcinoma; A randomised control trial comparing electrochemotherapy and surgery with five year follow up. European Journal of Surgical Oncology. 2020;46:847–54.

2. Spratt DE, Gordon Spratt EA, Wu S, et al. Efficacy of Skin-Directed Therapy for Cutaneous Metastases From Advanced Cancer: A Meta-Analysis. JCO. 2014;32:3144–55.

3. Quaglino P, Mortera C, Osella-Abate S, et al. Electrochemotherapy with Intravenous Bleomycin in the Local Treatment of Skin Melanoma Metastases. Ann Surg Oncol. 2008;15:2215–22.

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4. Campana LG, Valpione S, Mocellin S, et al. Electrochemotherapy for disseminated superficial metastases from malignant melanoma. British Journal of Surgery. 2012;99:821–30.

5. Kunte C, Letulé V, Gehl J, et al. Electrochemotherapy in the treatment of metastatic malignant melanoma: a prospective cohort study by InspECT. Br J Dermatol. 2017;176:1475–85.

6. Morley J, Grocott P, Purssell E, et al. Electrochemotherapy for the palliative management of cutaneous metastases: A systematic review and meta-analysis. European Journal of Surgical Oncology. 2019;45:2257–67.

7. Petrelli F, Ghidini A, Simioni A, et al. Impact of electrochemotherapy in metastatic cutaneous melanoma: a contemporary systematic review and meta-analysis. Acta Oncologica. 2021;1–12.

8. Weitman ES, Perez M, Thompson JF, et al. Quality of life patient-reported outcomes for locally advanced cutaneous melanoma. Melanoma Research. 2018;28:134–42.

9. Perone JA, Farrow N, Tyler DS, et al. Contemporary Approaches to In-Transit Melanoma. JOP. 2018;14:292–300.

10. Michielin O, van Akkooi A, Lorigan P, et al. ESMO consensus conference recommendations on the management of locoregional melanoma: under the auspices of the ESMO Guidelines Committee. Annals of Oncology. 2020;31:1449–61.

11. Sersa G, Miklavcic D, Cemazar M, et al. Electrochemotherapy in treatment of tumours. European Journal of Surgical Oncology (EJSO). 2008;34:232–40.

12. Quaglino P, Matthiessen LW, Curatolo P, et al. Predicting patients at risk for pain associated with electrochemotherapy. Acta Oncologica. 2015;54:298–306.

13. Campana LG, Testori A, Curatolo P, et al. Treatment efficacy with electrochemotherapy: A multi-institutional prospective observational study on 376 patients with superficial tumors. European Journal of Surgical Oncology (EJSO). 2016;42:1914–23.

14. Campana LG, Mocellin S, Basso M, et al. Bleomycin-Based Electrochemotherapy: Clinical Outcome from a Single Institution's Experience with 52 Patients. Ann Surg Oncol. 2009;16:191–9.

15. Gehl J, Sersa G, Matthiessen LW, et al. Updated standard operating procedures for electrochemotherapy of cutaneous tumours and skin metastases. Acta Oncologica. 2018;57:874–82.

16. Mir LM, Gehl J, Sersa G, et al. Standard operating procedures of the electrochemotherapy: Instructions for the use of bleomycin or cisplatin administered either systemically or locally and electric pulses delivered by the

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CliniporatorTM by means of invasive or non-invasive electrodes. European Journal of Cancer Supplements. 2006;4:14–25.

17. Miklavčič D, Mali B, Kos B, et al. Electrochemotherapy: from the drawing board into medical practice. BioMed Eng OnLine. 2014;13:29.

18. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer. 2009;45:228–47.

19. Rabin R, Charro F de. EQ-SD: a measure of health status from the EuroQol Group. Annals of Medicine. 2001;33:337–43.

20. Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health Qual Life Outcomes. 2007;5:70.

21. Fayers PM, Machin D. Quality of life: the assessment, analysis, and reporting of patient-reported outcomes. Third edition. Chichester, West Sussex, UK ; Hoboken, NJ: John Wiley & Sons Inc; 2016. 1 pag.

22. Szende A, Janssen B, Cabases J, curatori. Self-Reported Population Health: An International Perspective based on EQ-5D [Internet]. Dordrecht: Springer Netherlands; 2014 Available at: http://link.springer.com/10.1007/978-94-007-7596-1

23. Rapley M. Quality of Life Research [Internet]. 1 Oliver's Yard, 55 City Road, London England EC1Y 1SP United Kingdom: SAGE Publications, Ltd; 2003 Available at: http://methods.sagepub.com/book/quality-of-life-research

24. Bottomley A, Reijneveld JC, Koller M, et al. Current state of quality of life and patient-reported outcomes research. European Journal of Cancer. 2019;121:55–63.

25. Netuveli G, Blane D. Quality of life in older ages. British Medical Bulletin. 2008;85:113–26.

26. Rotunno R, Campana LG, Quaglino P, et al. Electrochemotherapy of unresectable cutaneous tumours with reduced dosages of intravenous bleomycin: analysis of 57 patients from the International Network for Sharing Practices of Electrochemotherapy registry. J Eur Acad Dermatol Venereol. 2018;32:1147–54.

27. Schadendorf D, Larkin J, Wolchok J, et al. Health-related quality of life results from the phase III CheckMate 067 study. European Journal of Cancer. 2017;82:80–91.

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28. Bottomley A, Coens C, Mierzynska J, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma (EORTC 1325-MG/KEYNOTE-054): health-related quality-of-life results from a double-blind, randomised, controlled, phase 3 trial. The Lancet Oncology. 2021;22:655–64.

29. Campana LG, Peric B, Mascherini M, et al. Combination of Pembrolizumab with Electrochemotherapy in Cutaneous Metastases from Melanoma: A Comparative Retrospective Study from the InspECT and Slovenian Cancer Registry. Cancers. 2021;13:4289.

30. Heppt MV, Eigentler TK, Kähler KC, et al. Immune checkpoint blockade with concurrent electrochemotherapy in advanced melanoma: a retrospective multicenter analysis. Cancer Immunol Immunother. 2016;65:951–9.

31. Theurich S, Rothschild SI, Hoffmann M, et al. Local Tumor Treatment in Combination with Systemic Ipilimumab Immunotherapy Prolongs Overall Survival in Patients with Advanced Malignant Melanoma. Cancer Immunol Res. 2016;4:744–54.

32. Campana LG, Miklavčič D, Bertino G, et al. Electrochemotherapy of superficial tumors – Current status: Seminars in Oncology. 2019;46:173–91.

33. Palliative Care - A Guide to Coping with Side Effects for People with Cancer and Their Families from the American Society of Clinical Oncology (ASCO).

34. Chiarion-Sileni V, Del Bianco P, De Salvo GL, et al. Quality of life evaluation in a randomised trial of chemotherapy versus bio-chemotherapy in advanced melanoma patients. European Journal of Cancer. 2003;39:1577–85.

35. Coates A, Thomson D, McLeod GRM, et al. Prognostic value of quality of life scores in a trial of chemotherapy with or without interferon in patients with metastatic malignant melanoma. European Journal of Cancer. 1993;29:1731–4.

36. Cormier JN, Davidson LN, Webster KA, et al. Development of a melanoma-specific subscale for the Functional Assessment of Cancer Therapy (FACT-Melanoma). JCO. 2004;22:8122–8122.

37. Moran C, Coroiu A, Körner A. Psychosocial distress in patients with cutaneous melanoma: validation of the Skin Cancer Index (SCI). Support Care Cancer. 2021;29:1005–14.

38. Prinsen CAC, de Korte J, Augustin M, et al. Measurement of health-related quality of life in dermatological research and practice: outcome of the EADV Taskforce on Quality of Life. J Eur Acad Dermatol Venereol. 2013;27:1195–203.

Accepted Article

This article is protected by copyright. All rights reserved

39. Finlay AY, Salek MS, Abeni D, et al. Why quality of life measurement is important in dermatology clinical practice: An expert-based opinion statement by the EADV Task Force on Quality of Life. J Eur Acad Dermatol Venereol. 2017;31:424–31.

40. Chernyshov PV, Lallas A, Tomas-Aragones L, et al. Quality of life measurement in skin cancer patients: literature review and position paper of the European Academy of Dermatology and Venereology Task Forces on Quality of Life and Patient Oriented Outcomes, Melanoma and Non-Melanoma Skin Cancer. J Eur Acad Dermatol Venereol. 2019;33:816–27.

41. Musoro ZJ, Hamel J-F, Ediebah DE, et al. Establishing anchor-based minimally important differences (MID) with the EORTC quality-of-life measures: a meta-analysis protocol. BMJ Open. 2018;8:e019117.

42. Peeters Y, Stiggelbout AM. Health State Valuations of Patients and the General Public Analytically Compared: A Meta-Analytical Comparison of Patient and Population Health State Utilities. Value in Health. 2010;13:306–9.

43. Gandhi M, Oishi K, Zubal B, et al. Unanticipated toxicities from anticancer therapies: Survivors' perspectives. Support Care Cancer. 2010;18:1461–8.

44. Haley AC, Calahan C, Gandhi M, et al. Skin care management in cancer patients: an evaluation of quality of life and tolerability. Support Care Cancer. 2011;19:545–54.

45. Bottomley A, Pe M, Sloan J, et al. Analysing data from patient-reported outcome and quality of life endpoints for cancer clinical trials: a start in setting international standards. The Lancet Oncology. 2016;17:e510–4.

46. Campana LG, Clover AJP, Valpione S, et al. Recommendations for improving the quality of reporting clinical electrochemotherapy studies based on qualitative systematic review. Radiology and Oncology. 2016;50:1–13.

47. Fallowfield LJ, Catt SL, May SF, et al. Therapeutic aims of drugs offering only progression-free survival are misunderstood by patients, and oncologists may be overly optimistic about likely benefits. Support Care Cancer. 2017;25:237–44.

48. Bridges JFP, Mohamed AF, Finnern HW, et al. Patients' preferences for treatment outcomes for advanced non-small cell lung cancer: A conjoint analysis. Lung Cancer. 2012;77:224–31.

Figure legends

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Figure 1. Comparison of the QoL between the InspECT melanoma cohort and the general population. EQ-5D utility score (**a**) and self-reported health state (**b**) by age in the InspECT cohort and the healthy population of the corresponding European Countries. *Self-Reported Population Health: An International Perspective based on EQ-5D. Agota Szende, Bas Janssen, Juan Cabase´s Editors. SpringerOpen. DOI 10.1007/978-94-007-7596-1. The InspECT registry includes patients from seven countries (the U.K., Italy, Ireland, Germany, Hungary, Denmark, Slovenia and Austria). The Austrian subgroup was excluded due to the low number (n=7).

Figure 2. Mean absolute values of the EQ-5D utility score (**a**), self-reported health state (**b**), and mean differences of EQ-5D utility score (**c**) and self-reported health state (**d**) compared to baseline values. Dashed lines in red indicate the minimal important difference (MID). P values refer to the comparison with baseline.

Figure 3. Variation in the EQ-5D-3L items following ECT. Each bar represents an HRQoL domain and intersects the average score reported by patients at baseline and during the follow-up. Bar grading: 1 = no problems; 2 = some problems; 3 = debilitating problems. Interpretation: smaller the area, the better the outcome.

Figure 4. Patient-reported outcomes after ECT according to response to treatment and ECOG PS at baseline. The left column reports the absolute values of EQ-5D utility score (**a,e**) and EQ-VAS self-reported health state (**c,g**); in the right column, the mean differences compared to baseline values of EQ-5D (**b,f**) and EQ-VAS (**d,h**). P values refer to intra-group comparison with the baseline values. The dashed lines in B,D,F,H represent the upper/lower threshold of minimal important difference (MID) *Legend*: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ECOG, Eastern Cooperative Oncology Group performance status.

Figure 5. Patient-reported outcomes after ECT according to previous systemic treatment and concomitant (started during follow-up) immunotherapy. The left column reports the absolute values of EQ-5D utility score (**a,e**) and EQ-VAS self-reported health state (**c,g**); in the right

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column, the mean differences compared to baseline values of EQ-5D (**b,f**) and EQ-VAS (**d,h**). P values refer to intra-group comparison with the baseline values. The dashed lines in b,d,f,h represent the upper/lower threshold of minimal important difference (MID) Legend: IT, immunotherapy.

Figure 6. Patient-reported outcomes after ECT according to AJCC melanoma disease stage and local toxicity (CTCAE v5.0). The left column reports the absolute values of EQ-5D utility score (**a,e**) and EQ-VAS self-reported health state (**c,g**); in the right column, mean differences compared to baseline values of EQ-5D (**b,f**) and EQ-VAS (**d,h**). P values refer to intra-group comparison with the baseline values. The dashed lines in b,d,f,h represent the upper/lower threshold of minimal important difference (MID). Legend: AJCC, American Joint Committee on Cancer; CTCAE, Common Terminology Criteria for Adverse Events.

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Table 1. Baseline demographic and clinical characteristics of 378 patients with superficially metastatic melanoma[†]

Factors	No. or median (% / range)
Gender	
M	180 (48)
F	198 (52)
Age (yrs)	75 (29-96)
ECOG PS[‡]	
0-1	294
2-4	58
Time since melanoma diagnosis (mos)	2 (0-36)
Disease stage	
III	309 (82)
IV	69 (18)
No. of skin mts/pt[§]	2 (1-7)
Tumour size (mm)[¶]	20 (5-700)
Size of lesions	
≤3 cm	264 (70)
>3 cm	114 (30)
Localisation	
Limbs	250 (66)
Trunk	78 (21)
Head-neck	50 (13)
Previous systemic tx	145 (38)
Concomitant IT[#]	80 (21)
Route of BLM	

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administration	
i.v	328 (87)
i.t	50 (13)

† Participating countries (and centres): Italy (Genova, Mirano, Novara, Padova, Pavia, Pisa, Roma, Torino), U.K. (Barts, Castle Hill, Liverpool, London St. Georges, London St. Thomas, London Queen Victoria, Manchester The Christie), Germany (Bochum, Mainz, Munich), Austria (Wels), Hungary (Szeged), Ireland (Cork), and Slovenia (Ljubljana). The 378 patients represent 76% of the InspECT register melanoma cohort with available QoL information. In the remaining 24% of the InspECT melanoma cohort, patient outcome was comparable to the present series: overall response rate, 79% (vs 80%); complete response rate, 45% (vs 47%); 1-year local progression-free survival rate 79% (vs 78%), grade-3 toxicity, 5.2% (vs 5%)

‡ Information available for 352 patients

§ Target lesions according to the Response Evaluation Criteria In Solid Tumors (RECIST) criteria

¶ Based on each patient's largest lesion

Concomitant IT indicates systemic immunotherapy administered since the first ECT

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Table 2. Univariate and multivariate analysis investigating the association of QOL variables and conventional clinical covariates on complete response to ECT in 378 melanoma patients

	Univariate			Multivariate		
	RR	95% C.I.	p	RR	95% C.I.	p
EQ-5D score	9.38	3.10-28.39	**<0.001**	14.76	2.81-77.60	**0.001**
EQ-VAS score	1.02	1.00-1.03	**0.032**	1	0.98-1.02	0.944
ECOG PS (0-1 vs 2-4	1.81	0.92-3.55	0.084			
T size (≤ 30 mm vs > 30 mm)	2.35	1.43-3.85	**<0.001**	1.54	0.85-2.79	0.155
No. of skin metastases	1.04	0.94-1.15	0.411			
Stage (III vs IV)	1.40	0.78-2.51	0.255			
Concomitant IT (yes vs no)	1.24	0.72-2.15	0.433			
Toxicity (yes vs no)	0.77	0.49-1.22	0.269			

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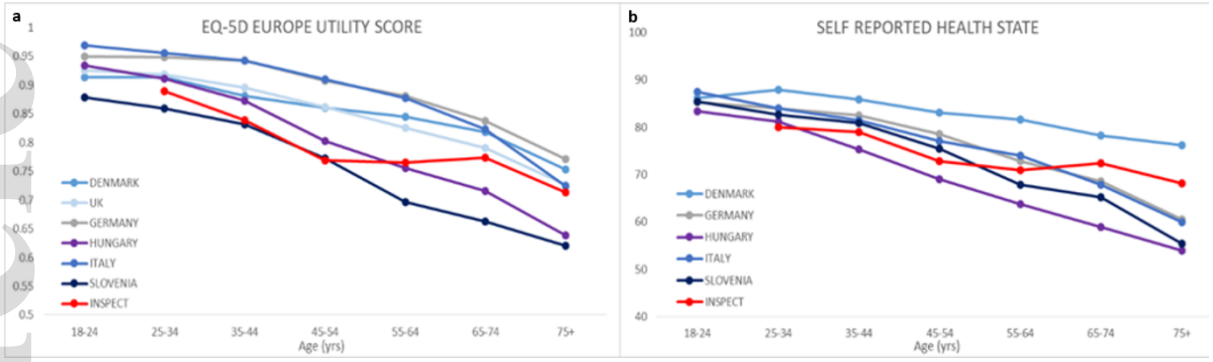
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Table 3. The area under the curve (AUC) for the patient-reported HRQoL using the EQ-5D-3L questionnaire. Interpretation: the higher the score, the better the outcome.

Group	Average AUC (SD)			
	EQ-5D	*p* value	**EQ-VAS**	*p* value
All patients (n=378)	0.72±0.20	n.a.	71±17	n.a.
ECOG PS 0-1 vs 2-4	0.75 ± 0.17 vs 0.55 ± 0.22	**<0.0001**	73 ± 16 vs 57 ± 11	**<0.0001**
Response to ECT CR vs PR+SD+PD	0.77 ± 0.17 vs 0.68 ± 0.21	**<0.0001**	75 ± 17 vs 68 ± 16	**0.0112**
Previous systemic Tx yes vs no	0.70 ± 0.18 vs 0.74 ± 0.20	0.1072	67 ± 16 vs 74 ± 16	**0.0024**
Concomitant IT yes vs no	0.75 ± 0.17 vs 0.72 ± 0.20	0.2654	72 ± 16 vs 71 ± 17	0.6392
Stage III vs IV	0.73 ± 0.20 vs 0.71 ± 0.16	0.4187	73 ± 16 vs 65 ± 17	**0.0166**
Local toxicity yes vs no	0.70 ± 0.20 vs 0.78 ± 0.19	**0.0012**	70 ± 15 vs 73 ± 19	0.3468

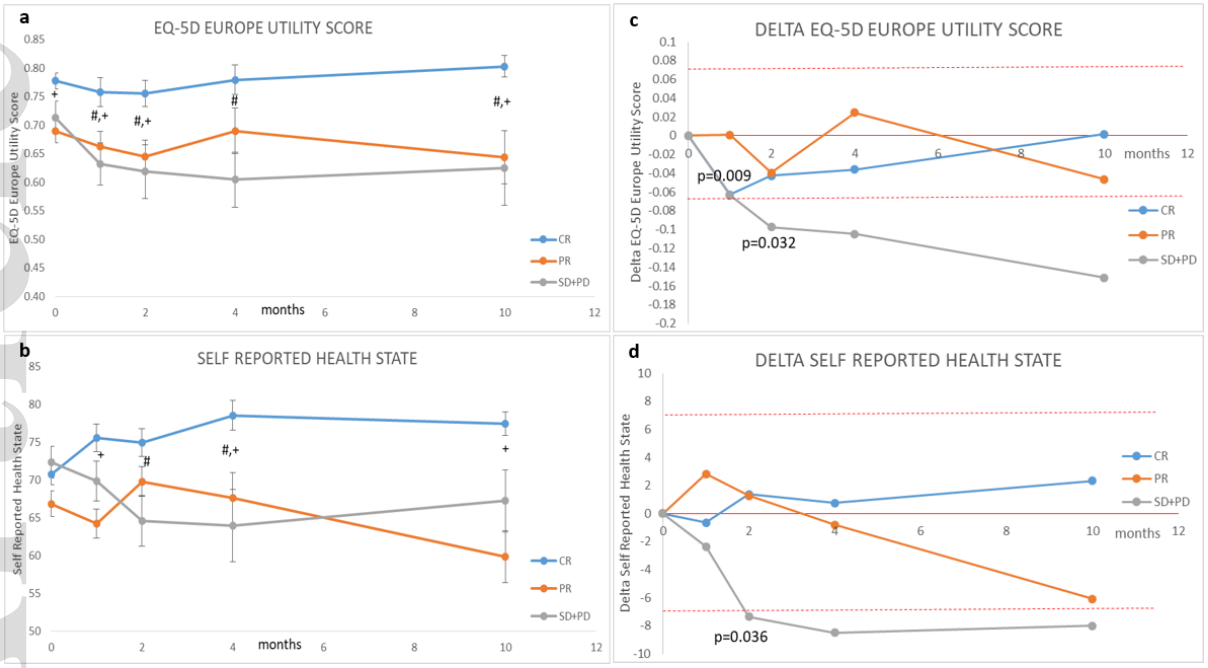
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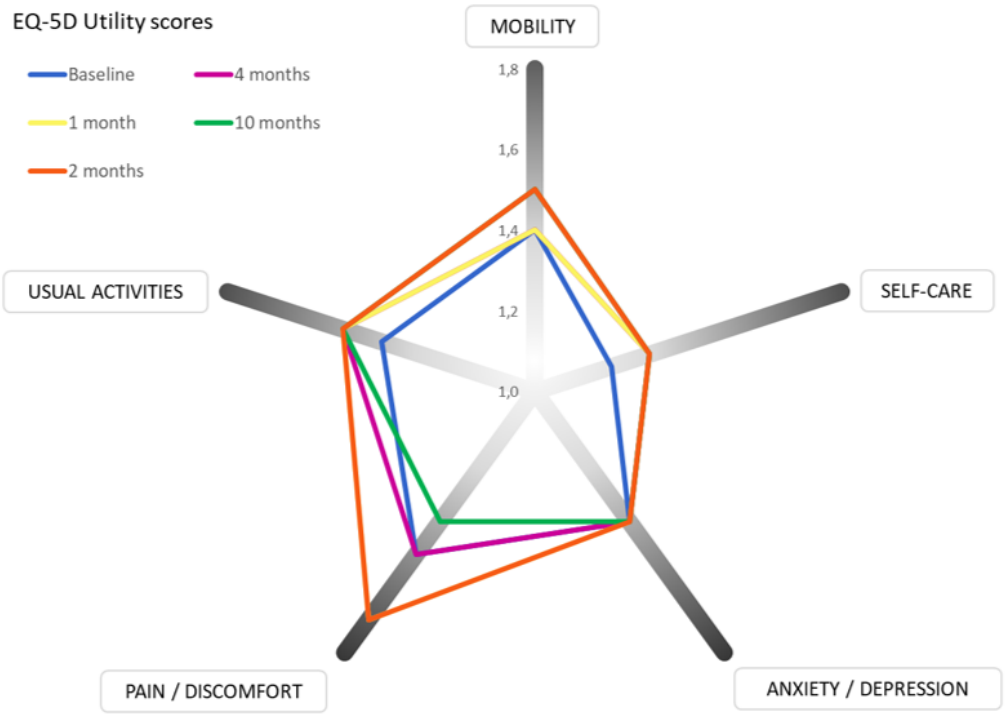
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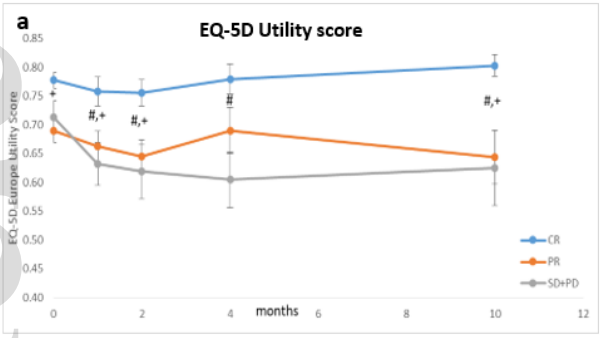
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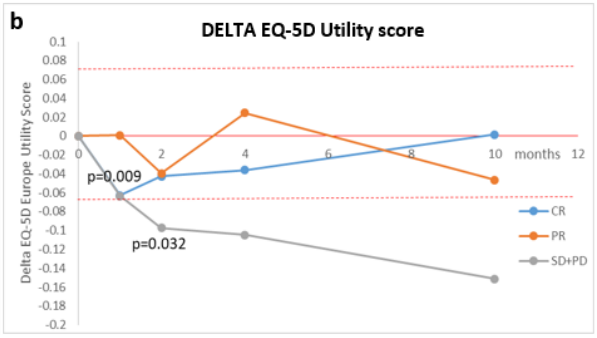
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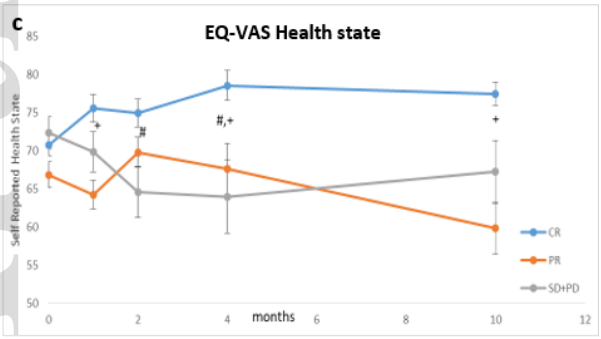


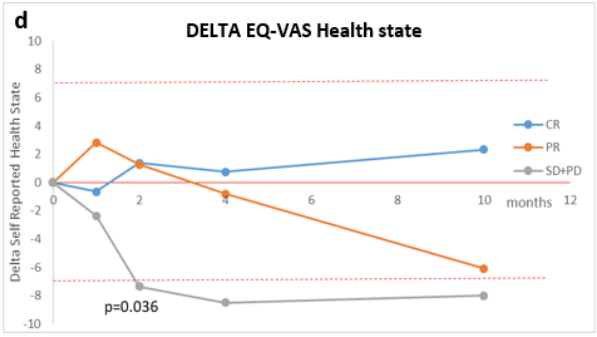
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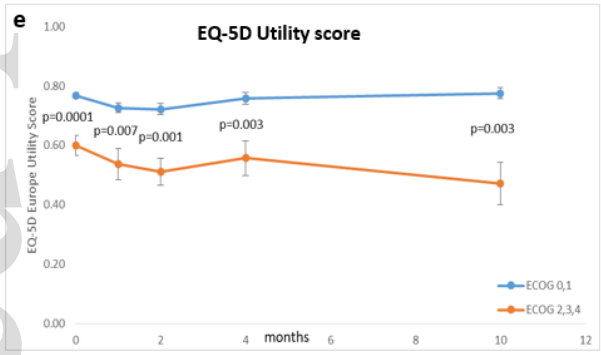
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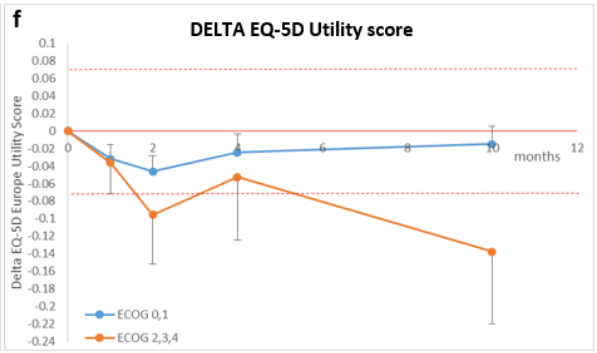


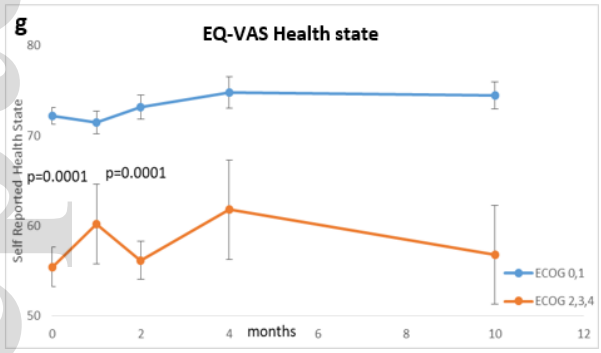


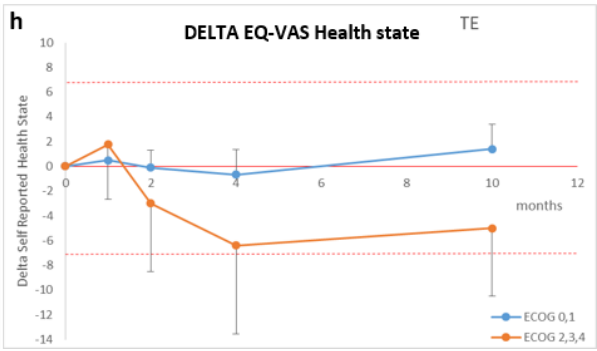






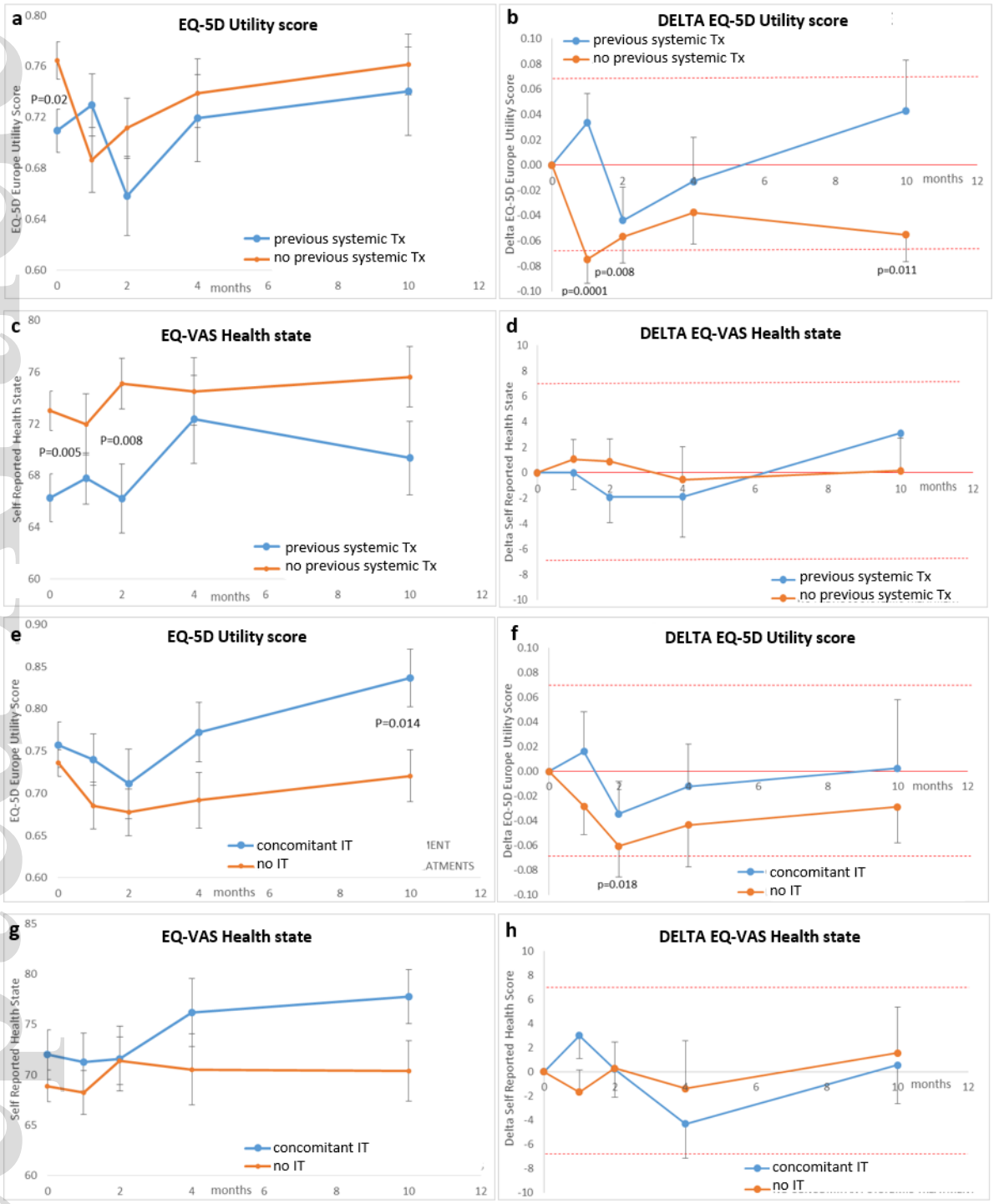






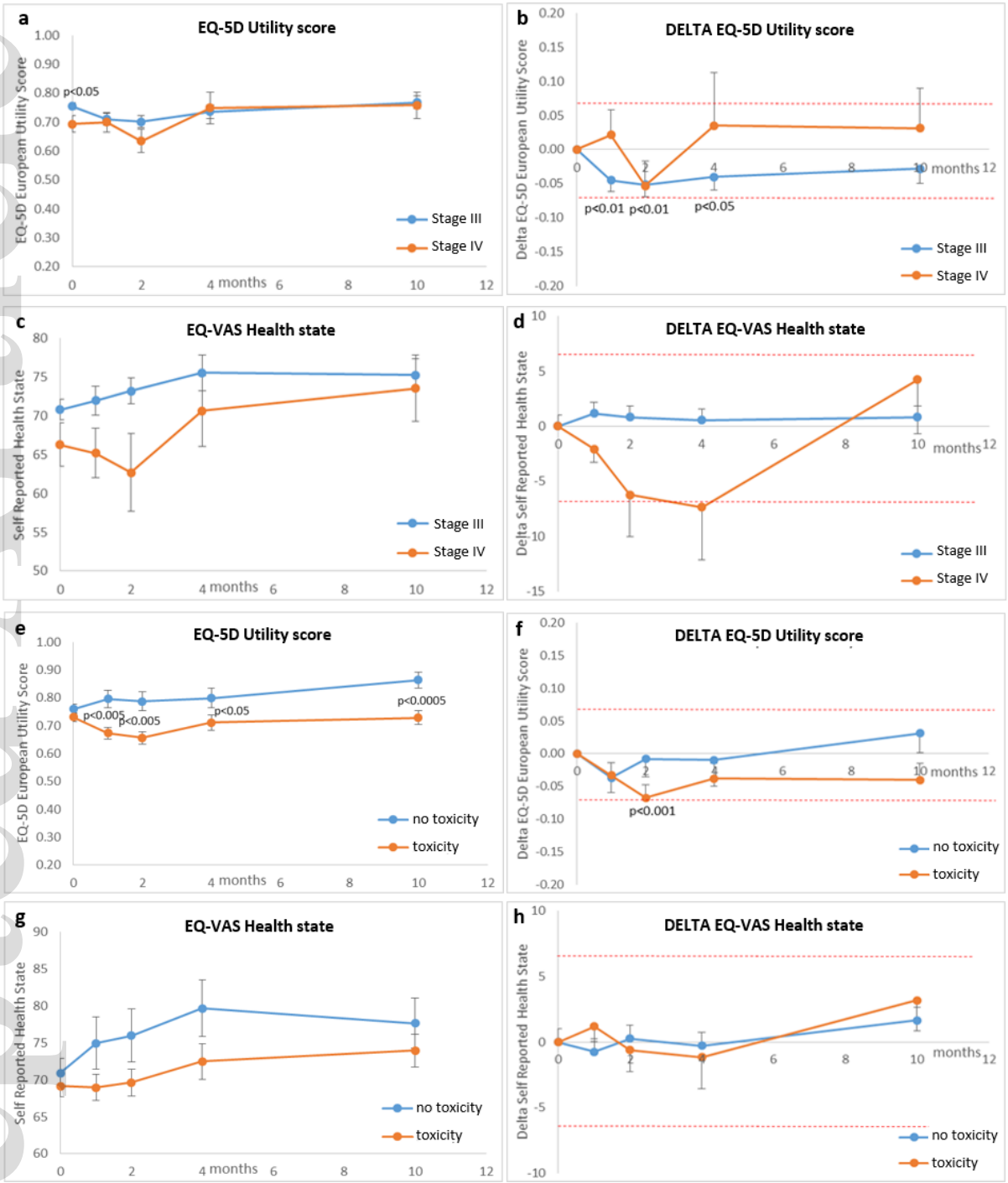
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