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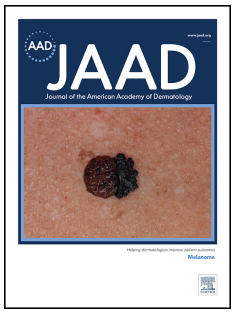

Predictors of surgical treatment burden, outcomes and overall survival in older adults with basal cell carcinoma: results from the prospective, multicenter BATOA cohort

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PII: S0190-9622(21)01034-3

DOI: https://doi.org/10.1016/j.jaad.2021.05.041

Reference: YMJD 16042

To appear in: *Journal of the American Academy of Dermatology*

Received Date: 15 December 2020

Revised Date: 24 April 2021

Accepted Date: 6 May 2021

Please cite this article as: van Winden MEC, Bronkhorst EM, Visch MB, Krekels GAM, van der Geer S, Damen GWJA, Amir A, Aben KKH, Gerritsen M-JJP, van de Kerkhof PCM, de Jong EMGJ, Lubeek SFK, Predictors of surgical treatment burden, outcomes and overall survival in older adults with basal cell carcinoma: results from the prospective, multicenter BATOA cohort, *Journal of the American Academy of Dermatology* (2021), doi: https://doi.org/10.1016/j.jaad.2021.05.041.

Capsule summary

- Basal cell carcinoma management in older adults can be challenging. In this study, patients ≥70 years experienced low overall surgical treatment burden and complications.
- Frailty-related factors were associated with increased treatment burden (instrumental activities of daily living [iADL] dependency and polypharmacy), and overall mortality (6.5%; comorbidities and iADL dependency).

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Funding: none.

Conflict of interest: S. Lubeek has acted as consultant and/or paid speaker for Leo Pharma and Sanofi Genzyme. All financial compensations were paid to the independent research fund of the department of dermatology of the Radboud university medical center Nijmegen, the Netherlands. All other authors have no conflict of interest to declare.

Prior presentation: Preliminary data was presented at a poster at the 28th European Academy of Dermatology and Venereology Congress, 2019.

Reprint request: Marieke van Winden.

Word count: 2499/2500 words

Abstract: 200/200 words

Capsule summary: 49/50 words

References: 29

Tables: 3

Figures: 2 (Figure 1A and Figure 1B)

Supplementary tables and figures: http://dx.doi.org/10.17632/bhwfs7xc9x.1

IRB approval status: yes, IRB has approved the study.

Attachements: STROBE checklist, IRB approval.

Key words

Skin cancer, keratinocyte carcinoma, basal cell carcinoma, surgery, Mohs micrographic surgery, conventional excision, traditional excision, facial surgery, older adults, elderly, aged, frailty, treatment burden, treatment outcomes, cosmetic result, complications, basal cell carcinoma recurrences, survival, mortality

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- Basal cell carcinoma management in older adults can be challenging. In this study, patients ≥70 years experienced low overall surgical treatment burden and complications.
- Frailty-related factors were associated with increased treatment burden (instrumental activities of daily living [iADL] dependency and polypharmacy), and overall mortality (6.5%; comorbidities and iADL dependency).

Abstract

Background: Incorporating patient-related factors associated with treatment outcomes could improve personalized care in older basal cell carcinoma (BCC) patients.

Objective: To evaluate and identify predictors for treatment burden, treatment outcomes and overall survival in patients ≥70 years, surgically treated for BCC in the head-and-neck area.

Methods: Data from the prospective multicenter BATOA ("BAsal cell carcinoma Treatment in Older Adults") cohort study was extracted to evaluate experienced treatment burden (visual analog scale 0-10cm; lower scores indicating higher treatment burden), treatment outcomes and mortality.

Results: 539 patients were included (median age: 78 years). Patients experienced a low overall treatment burden (median 8.6) and good cosmetic result. Predictors for higher treatment burden were instrumental activities of daily living (iADL) dependency, female sex, complications, tumor diameter, and polypharmacy. Thirty-five (6.5%) patients died (none BCC-related) within follow-up, predictors for mortality were increasing comorbidity index and iADL dependency. No difference in these outcomes were seen between Mohs micrographic surgery and conventional excision after correction for covariates. Age was not significantly associated with any outcome.

Limitations: A selection bias may exist due to the observational design.

Conclusion: BCC management decisions based on chronological age alone should be avoided, whereas more attention is recommended for patient-related factors. Based on these data, early BCC intervention is beneficiary for robust and fit patients or those experiencing symptoms.

Introduction

Basal cell carcinoma (BCC) is the most common type of skin cancer, frequently characterized as slowly growing, low-malignant and often initially asymptomatic.[1] However, BCCs can cause substantial long-term morbidity due to local tissue invasion and functional deterioration, especially in the head-and-neck area.[2] Due to the rising incidence of BCCs and the fact that BCCs are most frequently seen at older age, older adults with BCC comprise a large and rapidly growing population.[2] Optimal BCC management in older adults can be complex, balancing the risk of under- and overtreatment. It may be reasonable to forego treatment (and associated risks of discomfort, complications) when the remaining lifespan is expected to be shorter than the time to develop BCC-related symptoms (e.g. disfigurement, bleeding, infection).[3] However, both expected treatment burden and limited life expectancy (LLE) can be difficult to determine in the heterogenous geriatric population. Therefore, undertreatment may occur when patients are suboptimally treated due to misjudged LLE or expected treatment burden. It could be helpful to include frailty-related patient characteristics (e.g. multimorbidity and/or functional status) in medical decision-making, as frailty has been associated with increased mortality and complications rates in several medical fields.[4-6]

To optimize individualized medical decision-making, this study aimed to evaluate the treatment burden in older adults who were surgically treated for BCC in the head-and-neck area. Furthermore, treatment outcomes (complications, cosmetic outcome and recurrence risk), overall survival, and the identification of relevant predictors were studied. Study outcomes were compared between patients treated with Mohs micrographic surgery (MMS) and conventional surgical excision (CE).

Methods

Study Design and Participants

The BATOA (BATOA: "BAsal cell carcinoma Treatment in Older Adults") cohort is a prospective multicenter observational cohort study of older patients (aged ≥70 years) treated for BCC in the head-and-neck area. Although the BATOA cohort includes BCC patients treated with several treatment modalities, only patients who were surgically treated for a histologically proven BCC were included in the analyses described here. Patients who were treated for multiple tumors were enrolled only for the first tumor as described in the treatment plan. Patients unable to understand the study information (e.g. patients with dementia) were excluded. Patients were consecutively included in five medical centers (private practices, academic and general hospitals) in the Netherlands between November 2016 and February 2019 (eFigure 1). Approval of the Medical Ethical Committee was obtained from each participating center and written informed consent was obtained from all participants.

Outcome measures

The primary outcome was the experienced treatment burden, as indicated by patients on a visual analog scale (VAS; 0 to 10cm) 2-4 months after treatment; lower scores representing a higher treatment burden (eFigure 2). Open questions were added to allow patients to elaborate on their experience. A pilot study was performed with 33 geriatric patients and 7 health care providers were consulted to improve comprehensibility and wording of the questions and explanation. The VAS is a widely accepted method to evaluate surgical treatment outcomes and is commonly used because it is user-friendly, easily applicable and well validated for many treatment outcomes.[7,8]

Secondary outcomes were: complications (defined according to the Dutch Society of Dermatology and Venereology classification),[9] cosmetic results (VAS 0-10cm; higher scores representing a better cosmetic result), recurrences, overall survival and predictors for each outcome

measure, and differences in outcome measures between patients treated with MMS and those treated with CE.

Data collection

Treatment decisions (e.g. treatment with MMS or CE) were made prior to inclusion and were based on clinical judgement and in accordance to clinical guidelines, regardless of participation in this study. The following (frailty-related) data were systematically collected using structured data forms:

(i) patient-related characteristics including sex, age at time of surgery, history of keratinocyte cancer (KC) and subsequent therapies, Charlson comorbidity index (CCI; a weighted index with higher scores corresponding with poor survival, in particular at a score ≥3),[10-13] polypharmacy (defined as the chronic use of ≥5 medications with different ATC3 codes),[14,15] the Katz's index of activities of daily living (ADL;[16] patients were considered ADL dependent if they were unable to perform ≥1 activities independently),[17] Lawton and Brody's index of instrumental ADL (iADL;[18] patients were considered iADL dependent if they were unable to perform ≥1 activities independently), and travel distance to treatment center;

(ii) tumor-related characteristics including primary or recurrent tumor, tumor location (categorized according to cosmetic subunits)[19], histopathological subtype, tumor diameter;

(iii) treatment-related characteristics including treatment center, number of stages (in case of MMS), defect size, wound closure technique, histopathological clearance, and the physician performing the surgical procedure(s).

For all patients, a minimum follow-up period of 18 months was maintained. Follow-up data was extracted from medical patient charts, Personal Records Database (in Dutch: *"Basisregistratie*

Personen", BRP) and the Dutch nationwide network and registry of histopathology ("*Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief"; PALGA*).[20]

Statistical analyses

Data were analyzed using Statistical Package for Social Sciences (SPPS) Statistics for Windows, version 25.0 (IBM, Armonk, NY, U.S.A.) and R version 3.6.3 (The R Foundation for Statistical Computing, Vienna, Austria). Prior to inclusion, a minimum sample size of 227 patients per treatment modality was estimated to be able to detect a difference of 0.5 (5%) in treatment burden between the groups(standard deviation 1.9, alpha=0.05 and beta=0.2). Continuous variables were reported as mean (±SD) or median (interquartile range; IQR), when appropriate. Categorical variables were reported as frequencies and percentages. Univariate analysis was performed using a Student's t-test or Mann-Whitney U test, and the chi-square or Fisher's exact test. Multivariable analysis using quantile regression was performed to correct for the effect of various potentially relevant patient-, tumor-, and treatment characteristics on the median treatment burden and cosmetic result. A step-down procedure with optimal Akaike information criterion (AIC) as stopping criterion was used to identify predictors for treatment burden and cosmetic result. Logistic regression was used to correct for possible confounders regarding complications and to calculate odds ratios (ORs) and 95% confidence intervals (95%CI), using a step-down procedure with $p<0.1$ as stopping criterion. Kaplan-Meier curves were plotted to determine overall survival, and Cox regression was used to correct for confounding variables and to calculate hazard ratios (HRs) and 95%CIs for mortality prediction. Missing values were excluded. To ensure comparability between successive models, all model-based analyses were performed on cases that were complete regarding the covariates for the specific outcome.

Results

Study participants

A total of 539 patients were included with a median age of 78 years (IQR 74-83 years), 296 (54.9%) were treated with MMS and 243 (45.1%) with CE. . Most tumors (309; 57.3%) were ≥1 cm, 68 (12.6%) were ≥2 cm. Comorbidities were prevalent; 370 (70.6%) patients had a CCI ≥1, and in 166 (31.7%) patients a CCI ≥3 was seen. Baseline characteristics of the participants are summarized in Table I.

Treatment burden

Patients experienced a low overall treatment burden, with a median visual analogue scale (VAS)-score of 8.6 (IQR 7.3-9.4; higher values indicate a lower treatment burden). Overall, 420 (80.2%) patients experienced the treatment as expected, and valued the information given prior to surgery as sufficient. However, 72 (13.7%) patients experienced a longer duration of surgery than expected, and 55 (10.5%) patients experienced a more painful treatment than expected. As shown in Table II, predictors for higher experienced treatment burden were iADL dependency (effect=-0.42; 95%CI -0.82…-0.21, p<0.001), female sex (effect=-0.52, -0.81…-0.19, p=0.002), complications (effect=-0.84, -2.23-…-0.15, p=0.018), tumor diameter (effect=-0.021, -0.043…-0.003, p=0.024), and polypharmacy (effect=-0.31, -0.63-…-0.01, p=0.042). As complications were the only covariate that could not be assessed preoperatively, a sensitivity analysis was performed without including complications; similar outcomes were seen. No association was found for age, CCI, and other covariates presented in Table I. As presented in eFigure 3, no significant difference was seen between treatment burden after MMS or CE using univariate analyses (medians were 8.6 and 8.7 respectively, p=0.093). Furthermore, no significant difference was found between MMS and CE after correction for the covariates in Table II (effect=0.09; -0.21…0.33, p=0.551).

Treatment outcomes

Complications

As shown in eTable I, complications were seen in 52 (9.6%) patients. Significant predictors for complications were tumor diameter (OR 1.07; 1.03…1.11, p=0.001) and wound closure technique (OR 2.69 [healing through secondary intention vs. primary closure]; 1.19…6.10, p=0.017; and OR 4.98 [reconstructions vs. primary closure]; 2.49…9.98, p<0.001). The final multivariable model of the step-down procedure is presented in Table III and eTable II. After correction for these covariates, multivariable analysis showed no significant difference between complications after MMS vs. CE (OR 0.92; 0.46…1.81, p=0.800).

Cosmetic result

Overall, patients reported a good cosmetic result (median 8.5; 6.7-9.5, eFigure 4). Significant predictors for lesser cosmetic scores were female sex (effect=-0.74; -1.13…-0.30, p=0.001), method of closure (effect of healing through primary closure vs. secondary intention -0.56; -0.79…-0.15, p=0.007) and the occurrence of complications (effect=-0.91; -2.46…-0.17, p=0.016). No significant difference in cosmetic result was found between MMS and CE after correction for confounders identified by regression analyses (effect=0.15; -0.12…0.79; p=0.271).

Tumor recurrence

The mean follow-up time for tumor recurrence was 23.0±6.4 months. Three (0.6%) patients developed a recurrent BCC, all initially treated with CE, with postoperative histologically confirmed clearance. The time to recurrence was 9, 13 and 15 months.

<u>Overall survival</u>

Of all included patients, 35 (6.5%) died during follow-up, with a mean time until death of 14.0±5.4 months. No deaths were BCC-related. For the remaining patients, the mean follow-up for survival was 23.3±1.4 months. Predictors for all-cause mortality were increasing CCI (HR 1.30; 1.12…1.51, p<0.001), and iADL dependency (HR 3.21; 1.48…6.98, p=0.003; Figure 1). No significant difference

was seen between survival after MMS or CE after correction for confounders shown in eTable III (HR 1.69; 0.83…3.45, p=0.149). Outcomes were similar when looking at 1-year (n=13, 2.4%) and 2-year survival only.

Discussion

It seems essential to include treatment burden and its predictors in BCC management to improve time-to-benefit estimation in older adults.[21,22] Especially in frail older adults with a decreased functional reserve, hospital visits, surgical procedures and postoperative care can be overwhelming and cause substantial distress.[6,23] Remarkably, older adults included in this study experienced a low overall treatment burden (median VAS-score of 8.6; (IQR 7.3-9.4) and overall mortality (6.5%), and frailty-related patient characteristics were important predictors for higher treatment burden (iADL dependency and polypharmacy), and with overall mortality (comorbidities and iADL dependency).

Overall, the results of this study showed no reason to assume that surgical treatment of BCC in the head-and-neck area is too burdensome for patients with advanced age only. Moreover, despite the fact that MMS is more labor-intensive and time-consuming than CE,[12] multivariable analyses showed no significant difference between treatment burden, nor in the incidence of complications after MMS vs. CE. Whereas the results on complications are comparable with previous studies,[12,22,24,25] literature on BCC treatment burden is sparse.[21] The results of this study appear consistent with available studies reporting that older adults frequently experience surgical BCC treatment as satisfactory.[26-28] It should be noted that patient satisfaction is not entirely comparable with treatment burden; patients can be satisfied with overall clinical care and health care professionals, but still experience a high treatment burden due to the impact of treatment on their daily activities and social resources. Moreover, the impact of unsatisfactory cosmetic results should not be underestimated in older adults, as the patients included in this study regularly mentioned esthetic outcome as an important factor in overall treatment experience. Nonetheless, overall results of this study and previous studies indicate that older adults endure surgical BCC treatment well and chronological age should not lead to a priori rejection of certain treatment options. This too can be accentuated by the high overall survival seen in this study (93.5%) after a mean follow-up of 23.3 months. A possible explanation for this could be that patients treated for BCC can be presumed quite fit and generally high functioning (i.e. relatively few comorbidities and (i)ADL dependency) compared

with the overall population.[29] This is supported by a 16.6% lower 2-year mortality compared with Dutch citizens of the same age,[30] although these numbers are not entirely comparable due to the distribution of the data. Moreover, the baseline demographics of the included patients further emphasize the heterogeneity of the geriatric population and encourage individualized medical decision-making.

The predictors for higher treatment burden in this study consisted of iADL dependency, female sex, larger tumor diameter and polypharmacy. These findings could aid clinicians in advising those patients who may need extra measures to reduce the burden of therapy; for instance, extra postoperative care, home visits or help from medical caretakers, general practitioner or relatives. In line with several articles,[3,13,29,31] comorbidities (increasing CCI) and iADL dependency were significantly associated with increased overall (non-BCC-related) short-term mortality, although the study of Linos et al. indicated the CCI to be less accurate at estimating 5-year survival in a majority of the included patients.[12] Therefore, it remains difficult to estimate life expectancy and more research is highly needed to provide consensus in this field. Nonetheless, as both comorbidities and iADL dependency are frailty-related, frailty screening could aid in estimating patients' life expectancy in a more holistic approach,[23] although current experience in dermatology daily care is limited.[21,32] However, as chronological age was not identified as a significant predictor for treatment burden, complications, cosmetic result, or overall survival, physicians should refrain from making treatment decisions based solely on age, and preferably prioritize the consideration of frailty-related patient characteristics that could lead to adverse health outcomes.

The combination of overall low treatment burden and high overall survival leads us to believe that the surgical treatment choices have been adequate in this part of the BATOA cohort. As tumor growth was associated with higher treatment burden and complications, early BCC intervention is beneficiary for robust and fit patients or those experiencing symptoms. However, as currently much is still unknown concerning the natural course of BCCs, it remains difficult to estimate the time-to-benefit. Naturally, treatment choices should align with individual patient values, treatment goals and

preferences, especially when the life expectancy and time-to-benefit are roughly equal. Watchful waiting could be a suitable alternative for surgical BCC treatment in certain patients with LLE and higher odds of a high treatment burden, and if the burden of the tumor itself is low (e.g. no BCC-related burdensome symptoms). Currently, little data is available in guiding clinicians in which situations watchful waiting is an appropriate management option and more research clarifying this dilemma is essential.[21,22]

Certain limitations need to be addressed; a selection bias may exist due to the observational design of the study. However, the results presented here probably adequately represent daily clinical care, and correction for baseline differences was applied to reduce bias as much as possible. Of note, treatment burden was evaluated at one time point, whereas patient experiences might fluctuate over time. At the start of this study, no validated tools were available to evaluate surgical treatment burden, therefore a VAS scale was used after a pilot study to ensure comprehensibility. Also, future studies with adequate power and longer follow-up are needed to provide more information on recurrences and survival, as these results are probably influenced by the relatively short follow-up.[33] Moreover, any study using real world data is subject to a preselection of patients, as only patients who appear fit enough to undergo surgery were included in this study. Apparently, the preselection of patients as included in this cohort has been adequate, with overall adequate results on treatment burden, complications, cosmetic result and overall survival.

Conclusion

In conclusion, BCC management decisions merely on the basis of age as sole patient-related factor should be avoided, as chronological age showed no significant association with treatment burden, complications, cosmetic results and overall mortality. Moreover, using advanced age as an exclusion criterium could lead to a delay in adequate medical interference, leading to larger tumors and a subsequent higher chance of tumor-related complaints, complications and treatment burden. This study has identified important patient-related aspects which could aid in medical decision making: in

patients with higher CCI, iADL dependency and polypharmacy, the risks of treatment, including the treatment burden, might outweigh the benefits in individual cases. As it remains difficult to properly predict life expectancy, more research in this field is highly needed and determining which patients are too frail for surgery should not only include these frailty-related aspects, but also the treating physician's estimation of life expectancy, a discussion with patients about their goals of care, risks of treatment, and the common sequelae of BCC non-treatment with the estimated timeframe within which these sequelae may occur.

Acknowledgements

We would like to thank all patients who participated in this study and all health care professionals who enrolled patients or helped in data collection, in particular mrs. T. ten Broeke-van der Lee (Rijnstate Hospital), S. van Hees (MohsA clinics), F. Daniëls (MohsA clinics), drs. J.D. van der Waa (Mohsa clinics) drs. L.G.E. Lamboo (Queen Beatix Hospital, Winterswijk) and drs. T.B.J. Demeyere (PAMM Foundation, Eindhoven). Moreover, we would like to thank Dr. E.H. van den Bogaard (Radboudumc) for proofreading the manuscript. Written permission was obtained of all individuals included in the acknowledgements.

342 **Abbreviation list**

343 ADL: activities of daily living

344 AIC: Akaike information criterion

345 BATOA: “BAsal cell carcinoma Treatment in Older Adults”

346 BCC: basal cell carcinoma

347 CCI: Charlson comorbidity index

348 CE: conventional excision

349 CI: confidence interval

350 HR: hazard ratio

351 iADL: instrumental activities of daily living

352 IQR: interquartile range

353 LLE: limited life expectancy

354 MMS: Mohs micrographic surgery

355 OR: odds ratio

356 VAS: visual analog scale

357

References

1. Linos E, Berger T, Chren MM. Point: Care of potential low-risk basal cell carcinomas (BCCs) at the end of life: The key role of the dermatologist. *Journal of the American Academy of Dermatology.* 2015;73(1):158-161.
2. Lubeek SF, van Vugt LJ, Aben KK, van de Kerkhof PC, Gerritsen MP. The Epidemiology and Clinicopathological Features of Basal Cell Carcinoma in Patients 80 Years and Older: A Systematic Review. *JAMA dermatology.* 2017;153(1):71-78.
3. Lee SJ, Leipzig RM, Walter LC. Incorporating lag time to benefit into prevention decisions for older adults. *Jama.* 2013;310(24):2609-2610.
4. Hamaker ME, Vos AG, Smorenburg CH, de Rooij SE, van Munster BC. The value of geriatric assessments in predicting treatment tolerance and all-cause mortality in older patients with cancer. *The oncologist.* 2012;17(11):1439-1449.
5. Faller JW, Pereira DDN, de Souza S, Nampo FK, Orlandi FS, Matumoto S. Instruments for the detection of frailty syndrome in older adults: A systematic review. *PloS one.* 2019;14(4):e0216166.
6. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet (London, England).* 2013;381(9868):752-762.
7. Sinha S, Schreiner AJ, Biernaskie J, Nickerson D, Gabriel VA. Treating pain on skin graft donor sites: Review and clinical recommendations. *The journal of trauma and acute care surgery.* 2017;83(5):954-964.
8. Rhee JS, Sullivan CD, Frank DO, Kimbell JS, Garcia GJ. A systematic review of patient-reported nasal obstruction scores: defining normative and symptomatic ranges in surgical patients. *JAMA Facial Plast Surg.* 2014;16(3):219-225; quiz 232.
9. Dutch Society of Dermatology and Venereology. Nederlanse Vereniging voor Dermatology en Venereologie. [Complication regristration]. Utrecht, Dutch Society of Dermatology and

Venereology, 2012. Available from https://nvdv.nl/storage/app/media/2015-02-06-algemeen-lijst-complicatiesdefinities.pdf (in Dutch).

10. Sundararajan V, Henderson T, Perry C, Muggivan A, Quan H, Ghali WA. New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. *Journal of clinical epidemiology.* 2004;57(12):1288-1294.

11. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* 1987;40(5):373-383.

12. Linos E, Parvataneni R, Stuart SE, Boscardin WJ, Landefeld CS, Chren MM. Treatment of nonfatal conditions at the end of life: nonmelanoma skin cancer. *JAMA internal medicine.* 2013;173(11):1006-1012.

13. Charles AJ, Otley CC, Pond GR. Prognostic factors for life expectancy in nonagenarians with nonmelanoma skin cancer: Implications for selecting surgical candidates. *Journal of the American Academy of Dermatology.* 2002;47(3):419-422.

14. Dutch College of General Practitioners, Huisartsen Genootschap, Nederlandse Vereniging voor Klinische Geriatrie, Orde van Medisch Specialisten. [Multidisciplinary Guideline Polypharmacy in elderly], Utrecht: Dutch College of General Practitioners, 2012. Available from: https://www.nhg.org/sites/default/files/content/nhg_org/uploads/polyfarmacie_bij_ouderen.pdf (in Dutch).

15. Reeve E, Wolff JL, Skehan M, Bayliss EA, Hilmer SN, Boyd CM. Assessment of Attitudes Toward Deprescribing in Older Medicare Beneficiaries in the United States. *JAMA internal medicine.* 2018;178(12):1673-1680.

16. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of Illness in the Aged: The Index of ADL: A Standardized Measure of Biological and Psychosocial Function. *JAMA.* 1963;185(12):914-919.

17. Deckx L, van den Akker M, Daniels L, et al. Geriatric screening tools are of limited value to predict decline in functional status and quality of life: results of a cohort study. *BMC family practice.* 2015;16:30.

18. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist.* 1969;9(3):179-186.

19. Bolognia JL, Schaffer JV, Cerroni L. Dermatology. 4th ed. Philadelphia: Elsevier Saunders; 2018. p. 2429.

20. Casparie M, Tiebosch AT, Burger G, et al. Pathology databanking and biobanking in The Netherlands, a central role for PALGA, the nationwide histopathology and cytopathology data network and archive. *Cell Oncol.* 2007;29(1):19-24.

21. Lubeek SFK, Michielsens CAJ, Borgonjen RJ, Bronkhorst EM, van de Kerkhof PCM, Gerritsen MP. Impact of High Age and Comorbidity on Management Decisions and Adherence to Guidelines... *Acta dermato-venereologica.* 2017;97(7):825-829.

22. Leus AJG, Frie M, Haisma MS, et al. Treatment of keratinocyte carcinoma in elderly patients - a review of the current literature. *Journal of the European Academy of Dermatology and Venereology : JEADV.* 2020.

23. Soto-Perez-de-Celis E, Li D, Yuan Y, Lau YM, Hurria A. Functional versus chronological age: geriatric assessments to guide decision making in older patients with cancer. *The Lancet Oncology.* 2018;19(6):e305-e316.

24. Paradela S, Pita-Fernández S, Peña C, et al. Complications of ambulatory major dermatological surgery in patients older than 85years. *Journal of the European Academy of Dermatology and Venereology.* 2010;24(10):1207-1213.

25. Bouhassira J, Bosc R, Greta L, et al. Factors associated with postoperative complications in elderly patients with skin cancer: A retrospective study of 241 patients. *Journal of geriatric oncology.* 2016;7(1):10-14.

26. Arts LPJ, Waalboer-Spuij R, de Roos KP, et al. Health-Related Quality of Life, Satisfaction with Care, and Cosmetic Results in Relation to Treatment among Patients with Keratinocyte Cancer in the Head and Neck Area: Results from the PROFILES Registry. *Dermatology (Basel, Switzerland).* 2019:1-10.

27. Drew BA, Karia PS, Mora AN, Liang CA, Schmults CD. Treatment Patterns, Outcomes, and Patient Satisfaction of Primary Epidermally Limited Nonmelanoma Skin Cancer. *Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al].* 2017;43(12):1423-1430.

28. Stebbins WG, Gusev J, Higgins HW, 2nd, Nelson A, Govindarajulu U, Neel V. Evaluation of patient satisfaction with second intention healing versus primary surgical closure. *Journal of the American Academy of Dermatology.* 2015;73(5):865-867.e861.

29. Rogers EM, Connolly KL, Nehal KS, Dusza SW, Rossi AM, Lee E. Comorbidity scores associated with limited life expectancy in the very elderly with nonmelanoma skin cancer. *Journal of the American Academy of Dermatology.* 2018;78(6):1119-1124.

30. Statistics Netherlands. [Survival chances; gender, age]. Statistic Netherlands, 2020. Available from: https://opendata.cbs.nl/statline/#/CBS/nl/dataset/70701ned/table?fromstatweb (in Dutch). Accessed on 4-9-2020.

31. Pascual JC, Belinchon I, Ramos JM. Mortality after dermatologic surgery for nonmelanoma skin cancer in patients aged 80 years and older. *Journal of the American Academy of Dermatology.* 2013;69(6):1051-1052.

32. van Winden MEC, Garcovich S, Peris K, et al. Frailty screening in dermato-oncology practice: a modified Delphi study and a systematic review of the literature. *Journal of the European Academy of Dermatology and Venereology : JEADV.* 2021;35(1):95-104.

459 33. Mosterd K, Krekels GA, Nieman FH, et al. Surgical excision versus Mohs' micrographic surgery
460 for primary and recurrent basal-cell carcinoma of the face: a prospective randomised
461 controlled trial with 5-years' follow-up. *The Lancet Oncology.* 2008;9(12):1149-1156.

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464 Table I. Patient-, tumor and treatment characteristics of older adults (aged ≥70 years) surgically treated

465 for basal cell carcinoma in the head-and-neck area.

	Overall study population	MMS	CE	p-value
Patient characteristics				
Age[a] (years),				
Median (IQR)	78 (74-83)	77 (74-82)	79 (74-84)	0.008
Mean ± SD	78.6 ± 5.8	77.9 ± 5.4	79.4 ± 6.2	
Sex, n (%)				0.491
Male	304 (56.4)	163 (55.1)	141 (58.0)	
Female	235 (43.6)	133 (44.9)	102 (42.0)	
History of KC, n (%)	324 (60.7)	180 (61.9)	144 (59.3)	0.541
Previous KC, median (range)	3 (1-104)	3 (1-78)	3 (1-104)	
Previously treated with CE, n (%)	301 (93.5)	161 (90.4)	140 (97.2)	
Previously treated with MMS, n (%)	68 (21.3)	43 (24.4)	25 (17.4)	
Previously treated with RT, n (%)	17 (5.4)	3 (1.7)	14 (9.9)	
CCI[b],				
Median (IQR)	2 (0-3)	1 (0-3)	2 (0-3)	0.026
Mean ± SD	1.9 ± 1.9	1.7 ± 1.7	2.2± 2.0	
Polypharmacy[c], n (%)	264 (50.1)	144 (50.3)	120 (49.8)	0.899
ADL dependent[d], n (%)	112 (21.1)	56 (19.2)	56 (23.3)	0.250
iADL dependent[d], n (%)	222 (42.0)	126 (43.4)	96 (40.2)	0.447
Travel distance (km),				
Median (IQR)	11 (6-17)	11 (7-18)	9 (5-17)	0.023
Tumor characteristics				
Previous treatment, n (%)				0.002
Primary tumor	467 (86.6)	244 (82.4)	223 (91.8)	
Recurrent/residual tumor	72 (13.4)	52 (17.6)	20 (8.2)	
Tumor location, n (%)				<0.001
Forehead	171 (31.7)	77 (26.0)	94 (38.7)	
Peri-ocular	34 (6.3)	30 (10.1)	4 (1.6)	
Cheek	66 (12.2)	25 (8.4)	41 (16.9)	
Nose	145 (26.9)	117 (39.5)	28 (11.5)	
Peri-oral	20 (3.7)	14 (4.7)	6 (2.5)	
Chin	5 (0.9)	1 (0.3)	4 (1.6)	
Ear	37 (6.9)	19 (6.4)	18 (7.4)	
Neck	40 (7.4)	7 (2.4)	33 (13.6)	
Scalp	21 (3.9)	6 (2.0)	15 (6.2)	
BCC subtype, n (%)				<0.001
Mixed	156 (28.9)	68 (23.0)	88 (36.2)	
Nodular	206 (38.2)	114 (38.5)	92 (37.9)	
Micronodular	66 (12.2)	28 (9.5)	38 (15.6)	
Infiltrative	103 (19.1)	83 (28.0)	20 (8.2)	
Superficial	7 (1.3)	2 (0.7)	5 (2.1)	
Adenoid	1 (0.2)	1 (0.3)	0 (0.0)	
Maximum tumor diameter in mm,				
Median (IQR)	10 (7-15)	12 (8-18)	9 (6-12)	<0.001
Mean ± SD	12.1 ± 6.9	13.9 ± 7.9	9.9 ± 4.7	
Treatment characteristics				
Maximum defect diameter in mm[e], median (IQR)	NA	15 (11-24)	NA	NA
Number of stages[e], median (IQR)	NA	1 (1-2)	NA	NA
Wound closure technique, n (%)				<0.001
Primary closure	331 (61.4)	148 (50.0)	183 (75.3)	
Through secondary intention	97 (18.0)	71 (24.0)	26 (10.7)	
Reconstruction[f]	111 (20.6)	77 (26.0)	34 (14.0)	

Separate surgical procedure for wound closure or re-excision due to positive margins, n (%)	42 (7.8)	8 (2.7)	34 (14.0)	<0.001

Values may not add up due to missings and rounding. Abbreviations: ADL, Activities of Daily Living; BCC, basal cell carcinoma; CCI, Charlson Comorbidity Index; CE, conventional excision; iADL, instrumental activities of daily living; IQR, interquartile range; MMS, Mohs micrographic surgery; NA, not applicable; KC, keratinocyte cancer; RT, radiotherapy; SD, standard deviation.

[a] at time of treatment. The maximum age of the included patients was 95 years in both treatment groups.

[b] Charlson comorbidity index (CCI) is a weighted index, frequently used in geriatric medicine, with higher scores corresponding with poor survival, in particular at a score ≥3)[10-13]

[c] defined as the use of the chronic use of ≥5 medications with different ATC3 codes.[14,15]

[d] the Katz's index of activities of daily living (ADL)[16] comprise: bathing, dressing, transferring, toileting, continence and eating. Patients were considered ADL dependent if they were unable to perform ≥1 activities independently. Lawton and Brody's index of instrumental ADL (iADL) [18]comprise: telephone use, grocery shopping, preparing meals, housekeeping, laundering, using transportation, taking medication, and managing finances. Patients were considered iADL dependent if they were unable to perform ≥1 activities independently. When analyzing iADL according to sex (i.e. excluding meal preparation, housekeeping and laundering in men and excluding managing finances), 89 (30.7%) MMS patients were iADL dependent and 72 (30.1%) CE patients were iADL dependent.

[e] in case of MMS

[f] including both flaps and grafts.

Table II. Results of the step-down procedure used in multivariable analyses (quantile regression) of covariates possibly associated with the experienced treatment burden in older adults (aged ≥70 years) surgically treated for basal cell carcinoma in the head-and-neck area.

	Effect	95%CI	p-value
Patient characteristics			
Sex[a]	-0.52	-0.81…-0.19	0.002
History of KC	-0.19	-0.46…0.15	0.274
Polypharmacy[b]	-0.31	-0.63…0.01	0.042
ADL dependent[c]	0.26	-0.09…0.48	0.140
iADL dependent[c]	-0.42	-.0.82…-0.21	<0.001
Travel distance (km)	0.008	-.0.004…0.023	0.180
Tumor characteristics			
Maximum tumor diameter (mm)	-0.021	-0.043…-0.003	0.024
Treatment characteristics			
Wound closure technique			
Primary closure	1*		
Through secondary intention	0.26	-0.23…0.64	0.305
Reconstruction[d]	-0.39	-0.88…0.08	0.101
Complications	-0.84	-2.23…-0.15	0.018

All patient-, tumor- and treatment characteristics reported in Table I were initially included in the full multivariable quantile regression model. Final predictors as shown in this table were selected using a step-down procedure with optimal Akaike information criterion (AIC) as stopping criterion. Treatment burden was measured on a visual analog scale (0-10cm, lower scores representing a higher treatment burden). A negative effect listed here therefore indicates increasing treatment burden compared to the references status.

Abbreviations: 95%CI, 95% confidence interval; ADL, Activities of Daily Living; iADL, instrumental activities of daily living; KC, keratinocyte cancer.

* Reference status.

[a] Reference status is “male”, for all other categorized variables “no” was the reference status.

[b] defined as the chronic use of ≥5 medications with different ATC3 codes.[14,15]

[c] ADL: bathing, dressing, transferring, toileting, continence and eating. iADL: telephone use, grocery shopping, preparing meals, housekeeping, laundering, using transportation, taking medication, and managing finances. When analyzing iADL according to sex (i.e. excluding meal preparation, housekeeping and laundering in men and excluding managing finances), no differences in outcome measures were seen.

[d] including both flaps and grafts.

Table III. Results of the step-down procedure used in multivariable analyses (logistic regression) of covariates possibly associated with postoperative complications in older adults (aged ≥70 years) surgically treated for basal cell carcinoma in the head-and-neck area.

	OR	95% CI	p-value
Primary tumor	2.43	0.91…6.51	0.077
Tumor diameter (mm)	1.07	1.03…1.11	0.001
Wound closure technique			
Primary closure	1*		
Through secondary intention	2.69	1.19…6.10	0.017
Reconstruction[a]	4.98	2.49…9.98	<0.001

The potentially clinically relevant patient-, tumor- and treatment characteristics initially included in the logistic regression model were: age, sex, Charlson comorbidity index, Diabetes Mellitus type 2, polypharmacy, (instrumental) activities of daily living dependency, primary/recurrent tumor, tumor location**, BCC subtype, tumor diameter, individual treatment center, treatment modality, wound closure technique, and closure on a second hospital visit. Final predictors as shown in this table were selected using a step-down procedure with p<0.1 as stopping criterion. The chi square value for the Hosmer-Lemeshow Test was 4.349 (p=0.824); indicating support for the model. The pseudo R squared value was 0.148.

Abbreviations: OR, odds ratio; 95%CI, 95% confidence interval.

* Reference status.

** Tumor location was too detailed to include in the final multivariable analysis model, descriptives are shown in eTable II.

[a] including both flaps and grafts.

525 **Figure 1. Kaplan Meier-curve to indicate the survival estimates of the surgically treated patients in older**

526 **adults (aged ≥70 years) surgically treated for basal cell carcinoma in the head-and-neck area.**

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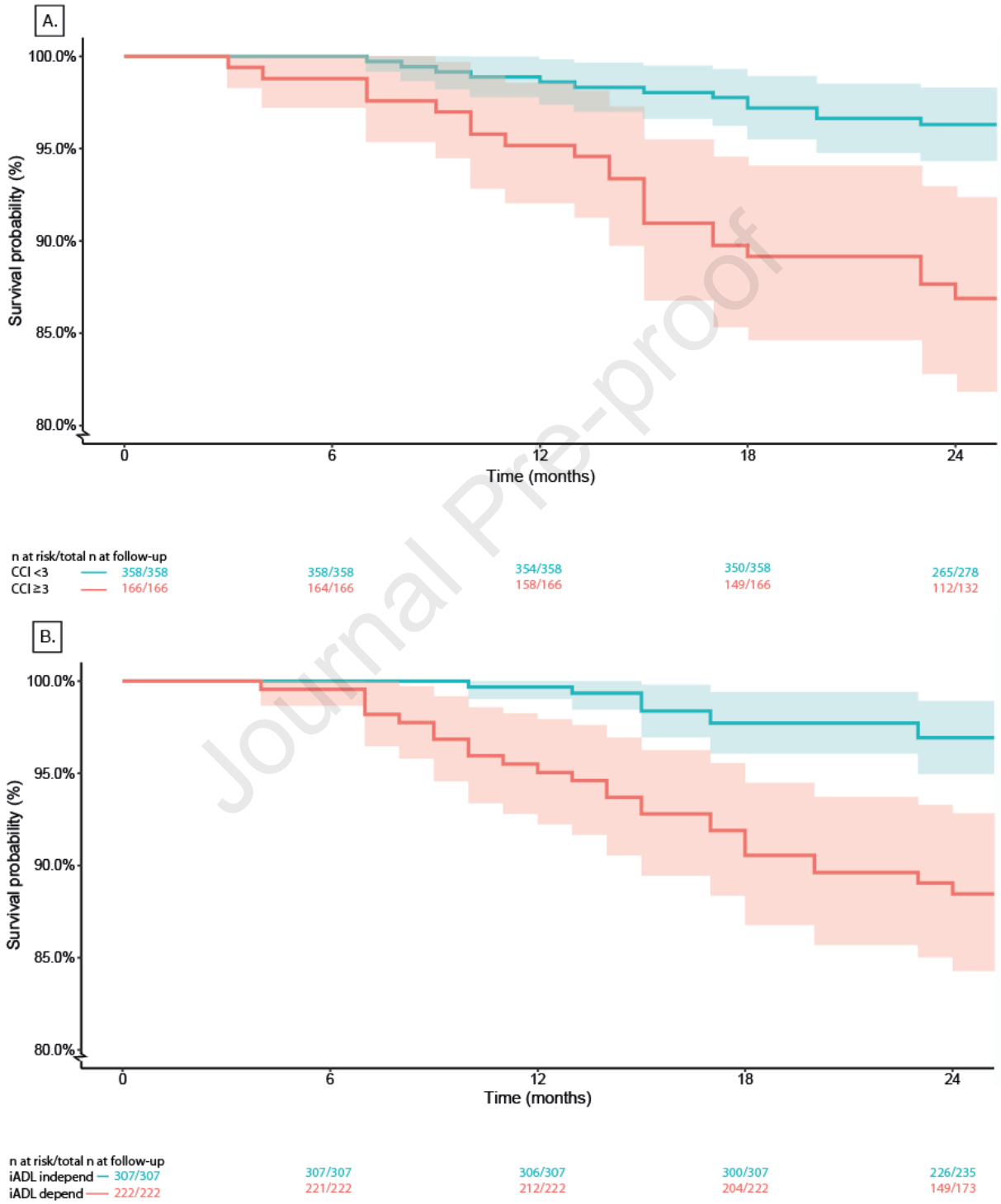

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530 Overall short-term survival with 95%CI for patients (aged ≥70 years) surgically treated for basal cell
531 carcinoma in the head-and-neck area, plotted by Charlson comorbidity index ≥3 (a) and instrumental
532 activities of daily living dependency (b). The Hazard ratios corrected for covariates are summarized in
533 eTable III.

534 Abbreviations: CCI, Charlson Comorbidity Index; depend, dependent; iADL, instrumental activities of
535 daily living; indep, independent.
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