Wide local excision for Merkel cell carcinoma of the lower extremity: A case report

YONG ZHANG, YAN SUN and JUEFEI MO

Department of General Surgery, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing 100053, P.R. China

Received June 25, 2022; Accepted September 8, 2022

DOI: 10.3892/etm.2022.11636

Abstract. Primary Merkel cell carcinoma (MCC) is rare and wide local excision is the primary method of treatment. However, no consensus has been reached on the best surgical approach and research is currently limited. The choice of surgical method depends on the experience of the surgeon and the situation of the patient. In the present study, the clinical data of a single case of primary MCC that was treated with wide local excision in June 2019 were retrospectively analyzed and the associated literature was reviewed. The patient underwent complete resection of the tumor, which extended 2 cm from the outer edge of the nodule and reached the subcutaneous fat layer. The wound was closed with a tension-relieving suture. The stitches were removed 15 days following surgery and the wound had healed adequately. No recurrence occurred during 30 months of follow-up. However, further multi-center prospective randomized clinical trials are required for further investigation.

Introduction

Surgical resection is the primary method for the treatment of Merkel cell carcinoma (MCC). However, due to the rare occurrence of this disease, high-quality clinical studies are lacking and treatment recommendations for MCC are complex and varied. Treatment approaches include wide local excision, Mohs surgery, radiotherapy and immunotherapy, as well as different combinations of these treatments (1). For wide local excision, the optimal margin width for primary MCC remains to be fully determined. Surgeons frequently trust their own judgment to try to maximize outcomes while minimizing morbidity (2). Furthermore, recent advances in immunotherapy for the treatment of metastatic melanoma have prompted the application of immunotherapy in MCC. Therefore, the optimal method of treatment for MCC remains to be determined. In the present study, a case of MCC was treated with extended resection and the desired efficacy was achieved. Combined with the relevant literature, the present study may provide a reference for the surgical treatment of MCC.

Correspondence to: Professor Juefei Mo, Department of General Surgery, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, 5 Beixiange Street, Xicheng, Beijing 100053, P.R. China
E-mail: dfree614@sina.com

Key words: Merkel cell carcinoma, surgery, wide local excision, resection margins, case report

Case report

A 90-year-old female patient was admitted to Guang'anmen Hospital (Beijing, China) in April 2019 with a mass on the right thigh. At the time, a fingernail-sized mass was found in the middle and lower parts of the right medial thigh but this was not documented. Subsequently, the size of the mass gradually increased, which was accompanied by itching, no tenderness and a dark red color. The patient had a history of hypertension, hyperthyroidism, glaucoma, cataract and a surgical history of gallstones and hemorrhoids. The patient denied any history of local trauma and had no family history of similar diseases. Physical examination demonstrated no notable abnormalities, no enlargement of the left popliteal fossa and the inguinal lymph nodes were palpable. A specialist examination demonstrated that the lower limbs of the patient were symmetrical in shape. The mass was on the right pretibial thigh and was accompanied by a 3x3-cm dark red nodule, which was ~8 cm above the knee with clear boundaries. The skin had a smooth, fixed basal surface and was visibly dry with flaking. There was no tenderness, the temperature of the skin was normal and there was no swelling. Furthermore, there was no canker seepage and no smell was observed (Fig. 1A). MRI demonstrated a space-occupying lesion rich in blood supply in the subcutaneous adipose layer of the right pretibial thigh (Fig. 1B and C). Under local infiltration anesthesia, complete resection of the tumor was performed using a 2-cm margin from the outer edge of the nodule. This reached the subcutaneous adipose layer and was sutured using a tension-relieving suture (Fig. 1D-G). The tissues were fixed with 4% paraformaldehyde, embedded in paraffin, sectioned at 4 μm, and then stained with hematoxylin for 5 min and eosin for 15 min at room temperature. Histopathology demonstrated that the epidermis was atrophied and thinned and the tumor cells in the dermis were distributed in clumps. Furthermore, the tumor cells were arranged in cords or adenoids. The cells were

notably deformed and there were myxoid deposits surrounding the cells (Fig. 2A-D). For immunohistochemistry (IHC), the paraffin slices were sectioned at a thickness of 4 μm, deparaffinized and rehydrated, followed by citrate-EDTA antigen retrieval. After peroxide block, samples were incubated with primary antibodies overnight at 4˚C and then with horseradish peroxidase-conjugated goat antirabbit immunoglobulin G (cat. no. DS-9800; Leica Biosystems, Inc.) for 30 min at 37˚C. The corresponding primary antibodies used in the experiments were as follows: Cytokeratin 20 antibody (cat. no. ZA-0574), CD56 antibody (cat. no. ZM-0057), chromogranin A antibody (cat. no. ZA-0507), synaptophysin antibody (cat. no. ZA-0506; all from OriGene Technologies, Inc.). The sections were then stained with a diaminobenzidine color kit (cat. no. ZLI-9017; OriGene Technologies, Inc.) and with hematoxylin for 5 min. The process of secondary antibody staining was based on the BOND-MAX Fully Automated IHC Stainer (Leica Biosystems). IHC staining demonstrated that the tumor tissue was positive for cytokeratin 20, CD56, chromogranin A and synaptophysin (Fig. 2E-H). The diagnosis was determined to be MCC. The stitches were removed 15 days after surgery and the wound healed adequately. There was no recurrence after 30 months of follow-up.

Discussion

MCC is a rare and aggressive cutaneous neuroendocrine tumor, originally described by Toker (3) as a trabecular carcinoma of the skin. However, the incidence of MCC continues to increase, which is mainly due to the aging population. A 95% increase in the incidence of MCC was reported in the US from 2000 to 2013 (4). MCC typically occurs in areas of the skin that are exposed to sunlight, such as the head, neck and limbs, in middle-aged and elderly patients. MCC may also be associated with immunosuppression and genetic mutations caused by Merkel cell polyomavirus infection (5,6). There is currently a lack of high-quality trials and literature, and further research into treatment options is required in order to improve the clinical outcomes of MCC.

At present, the initial management of primary MCC involves definitive resection of the primary tumor. However, the most optimal surgery for the treatment of MCC remains controversial. When selecting a specific surgical margin width for primary MCC, surgeons frequently rely on their own judgment to maximize prognosis while minimizing morbidity. Due to the high risk of local recurrence of MCC, surgical guidelines emphasize complete resection of the tumor during a one-stage operation to ensure surgical margin purity is clinically feasible (7). More specifically, it was previously recommended that the surgical margin width should be 3 cm (8). However, resection margins of >2 mm frequently require skin transplantation or flap reconstruction to close the wound (9), which markedly affects physical appearance. Transplantation or flap closure also increase postoperative morbidity and the financial cost to the patient. Furthermore, MCC is highly radiosensitive and radiotherapy following resection improves local area control and the overall survival rate (10). Perez and Zager (2) determined that there were no significant differences in local recurrence, disease-specific survival or overall survival among cases with a margin width of 1, 1.1-1.9 or ≥2 cm. Therefore, this may indicate that a resection margin of ≥3 cm may not be necessary.

According to the current National Cancer Center Network guidelines, the standard treatment for primary MCC is extensive local resection combined with adjuvant radiotherapy, with a specific resection margin of 1-2 cm (11). Results of a previous study demonstrated that the clinical local recurrence rate is 4.2-31.7% (12). These rates may be due to patients being treated without adjuvant radiation therapy, rapid growth and metastases of MCC, and the retrospective nature of previous studies. Furthermore, poor local control may be due to a positive margin caused by incomplete resection. The positive margin rate may reach 10.4% following extensive local resection derived from larger resection in more aggressive-appearing lesions (2). In addition, a false-negative margin may occur due to the standard pathological margin examination evaluating <1% of the surgical margin (13). Furthermore, a competing risk model was used to directly compare different resection margins based on stratified patients with MCC and this analysis removed the influence of non-cancer-related deaths on the outcome. These results demonstrated that patients <60 years of age with a tumor diameter of ≤5 cm (T1/2) and patients with a resection margin >2 cm who underwent early adjuvant radiotherapy exhibited improved survival rates. Furthermore, in patients >75 years of age, extensive resection was associated with a lower survival rate and complications were also more likely to occur. A resection margin ≤1 cm may be efficient for stage III MCC. In addition, the results of surgical resection in T3, T4 or stage IV MCC were not clear. Therefore, selecting the optimal surgical approach largely depends on the individual situation of the patient (14). Previous studies have demonstrated that there should be a safe margin of at least 1 cm in stage I disease and a larger margin of at least 2 cm in higher stages (5,15). In summary, extensive local resection using margins of 1-2 cm remains the standard surgical technique (16), particularly in stage I/II MCC. In higher stages of MCC, clear conclusions were difficult to obtain. However, a larger margin should not be used in order to not impede postoperative radiotherapy and operative complications are likely to occur.

For tissue preservation, Mohs or modified Mohs surgery may be performed. However, this is more likely to be performed for stage I/II MCC on the head or neck and sentinel lymph node biopsies should be performed as a priority (17). Furthermore, Mohs micrography supports a 100% margin assessment and reduces the chance of residue. In a retrospective study, Terushkin *et al* (13) reported that Mohs micrography for the treatment of early stage I/II MCC may achieve survival rates comparable to extensive local resection and/or adjuvant radiotherapy, without the requirement for additional radiotherapy or reoperation to further treat local recurrence. Similarly, a large-scale retrospective study from the National Cancer Database demonstrated that there was no difference in survival between patients who underwent Mohs micrography or extensive local resection for early stage I/II MCC (18). According to the European interdisciplinary consensus (19), the immunohistochemistry needed for the diagnosis of MCC requires specific staffing and technical support during Mohs surgery (20), in case of residual tumor cells in atypical patients. Furthermore, researchers have questioned the potential correlation between Mohs surgery with increased

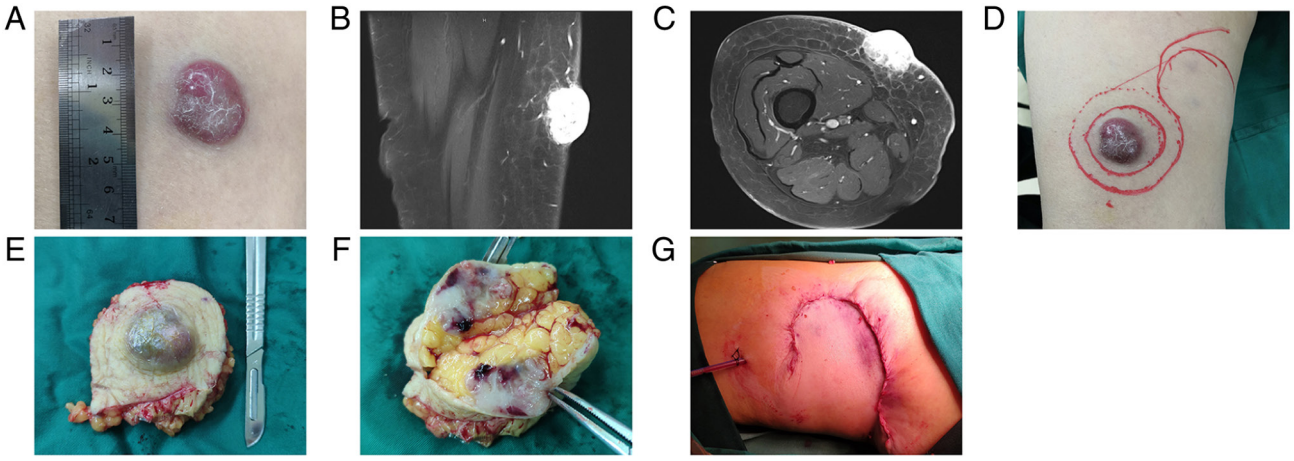

Figure 1. Intraoperative presentation. (A) Image of the 3x3 cm cutaneous tumor on the right thigh. (B) Sagittal MRI. (C) Transverse MRI. (D) A 2-cm resection margin. (E) Complete resection of the tumor. (F) Resection margin reached the subcutaneous adipose layer. (G) Tension-relieving suture.

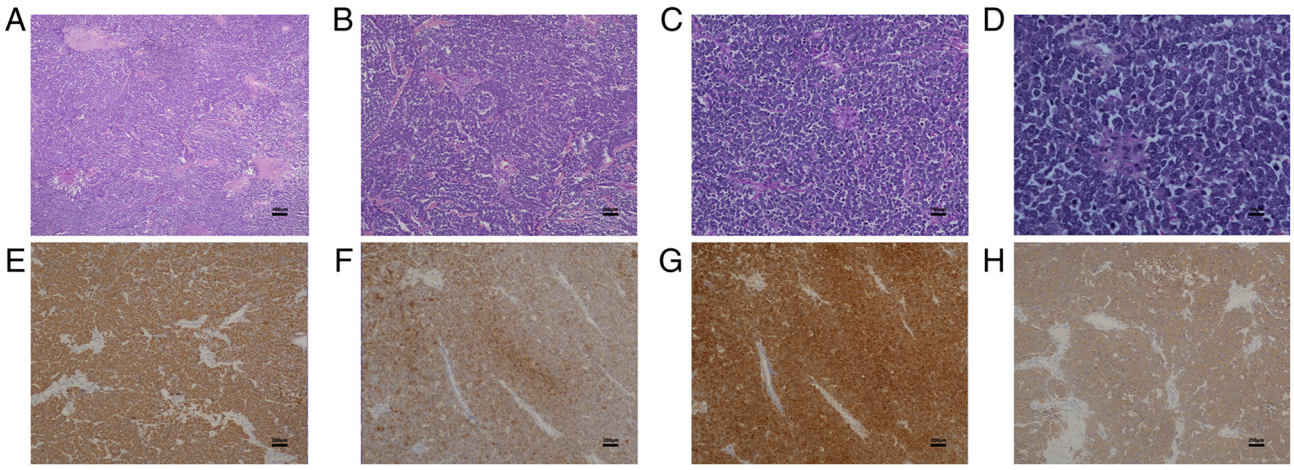

Figure 2. Pathology and immunohistochemistry of the lesion. (A-D) H&E staining of the excised tumor at magnifications of (A) x40, (B) x100, (C) x200 and (D) x400. Immunohistochemical staining for (E) cytokeratin 20(+), (F) neural cell adhesion protein (CD56) (+), (G) chromogranin A(+) and (H) synaptophysin(+) (scale bar, 200 μm).

tumor metastasis (21). In high-risk basal cell carcinoma and squamous cell carcinoma, Mohs surgery demonstrates notable advantages; however, no guidelines or consensus for Mohs surgery for MCC have been established. Therefore, Mohs surgery remains a viable alternative option. Previous research has also emphasized that biopsy staging should be performed in the tumor center area.

Recent advances in immunotherapy for the treatment of metastatic melanoma have prompted its application in MCC. Results of a previous meta-analysis demonstrated that immunotherapy was safe and effective in reducing the tumor diameter with a durable response rate (22). At present, immune checkpoint inhibitors (ICIs) exhibit no clear advantage as an adjuvant therapy and programmed cell death protein-1/programmed cell death-ligand 1 inhibitors are still considered first-line treatment options for advanced MCC (16). Furthermore, pembrolizumab and avelumab have been approved by the Food and Drug Administration for the treatment of advanced MCC (16,23). In a previous study, results were obtained in a multicenter, phase II, non-controlled study using 26 patients who received a dose of 2 mg/kg pembrolizumab every 3 weeks (23). After expanding the cohort to 50 patients, the overall response rate (ORR) was stable at 56% and the median pathological complete response was 16.8 months (24). In the phase II JAVELIN Merkel 200 clinical trial, 88 participants with advanced stage IV MCC received chemotherapy more than once. The results of the trial demonstrated a pathological complete response rate of 26% at 24 months and 21% at 36 months. The ORR at 36 months was 32, and 31% at 42 months when combined with a 1-h intravenous infusion of 10 mg/kg avelumab every 2 weeks (25). Furthermore, the efficacy of ipilimumab, INCMGA00012 and ICIs in combination is currently being investigated. There is insufficient evidence concerning the efficiency of neoadjuvant and adjuvant therapies in combination. In a recent phase I/II study comprising 39 patients with operable MCC, nivolumab was administered 4 weeks prior to surgery (26). Although pathological complete response is the main desired outcome, further clinical trials are required and numerous clinical studies using nivolumab, pembrolizumab and avelumab for the treatment of stage I-III MCC are in progress. Research into numerous immunotherapies has previously provided novel treatment strategies (16).

In the present study, the advanced age and MCC stage of the patient was considered and a wide local excision using a 2-cm resection margin was performed. The patient refused to receive further adjuvant radiotherapy. Furthermore, the follow-up period was 30 months following surgery and no recurrence or complications occurred.

At present, the surgical treatment of MCC is not based on high levels of clinical evidence. Extensive local resection using a 1-2 cm margin remains the standard surgical technique, particularly in stage I/II MCC. A larger resection margin is not recommended, as it may delay radiotherapy or lead to further complications. In addition, immunotherapy-based research has provided novel treatment strategies. In the future, multicenter prospective randomized clinical trials are required to determine the optimal operative and perioperative plan, following a comprehensive assessment of the local recurrence rate, survival rate and disease-specific survival rate (2).

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions

YS and YZ performed the data analyses and wrote the manuscript. JM performed the surgery and contributed to the original conception of the study. YZ and JM confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Guang'anmen Hospital, China Academy of Chinese Medical Sciences (Beijing, China; approval no. 2022-SDTS-06).

Patient consent for publication

Written informed consent for the publication of the patient's clinical information and images was obtained from the patient.

Competing interests

The authors declare that they have no competing interests.

References

1. Harvey JA, Mirza SA, Erwin PJ, Chan AW, Murad MH and Brewer JD: Recurrence and mortality rates with different treatment approaches of Merkel cell carcinoma: A systematic review and meta-analysis. Int J Dermatol 61: 687-697, 2022.
2. Perez MC and Zager JS: Aso author reflections: Resection margins in merkel cell carcinoma: Is a 1 cm margin wide enough? Ann Surg Oncol 25 (Suppl 3): S901, 2018.
3. Toker C: Trabecular carcinoma of the skin. Arch Dermatol 105: 107-110, 1972.
4. Paulson KG, Park SY, Vandeven NA, Lachance K, Thomas H, Chapuis AG, Harms KL, Thompson JA, Bhatia S, Stang A and Nghiem P: Merkel cell carcinoma: Current US incidence and projected increases based on changing demographics. J Am Acad Dermatol 78: 457-463.e2, 2018.
5. Schadendorf D, Lebbe C, Zur Hausen A, Avril MF, Hariharan S, Bharmal M and Becker JC: Merkel cell carcinoma: Epidemiology, prognosis, therapy and unmet medical needs. Eur J Cancer 71: 53-69, 2017.
6. Rollison DE, Giuliano AR and Becker JC: New virus associated with merkel cell carcinoma development. J Natl Compr Canc Netw 8: 874-880, 2010.
7. Bichakjian CK, Olencki T, Alam M, Andersen JS, Berg D, Bowen GM, Cheney RT, Daniels GA, Glass LF, Grekin RC, *et al*: Merkel cell carcinoma, version 1.2014. J Natl Compr Canc Netw 12: 410-424, 2014.
8. Becker J, Mauch C, Kortmann RD, Keilholz U, Bootz F, Garbe C, Hauschild A and Moll I: Short german guidelines: Merkel cell carcinoma. J Dtsch Dermatol Ges 6 (Suppl 1): S15-S16, 2008 (In English, German).
9. Doepker MP, Thompson ZJ, Fisher KJ, Yamamoto M, Nethers KW, Harb JN, Applebaum MA, Gonzalez RJ, Sarnaik AA, Messina JL, *et al*: Is a wider margin (2 cm vs. 1 cm) for a 1.01-2.0 mm melanoma necessary? Ann Surg Oncol 23: 2336-2342, 2016.
10. Strom T, Carr M, Zager JS, Naghavi A, Smith FO, Cruse CW, Messina JL, Russell J, Rao NG, Fulp W, *et al*: Radiation therapy is associated with improved outcomes in merkel cell carcinoma. Ann Surg Oncol 23: 3572-3578, 2016.
11. Bichakjian CK, Olencki T, Aasi SZ, Alam M, Andersen JS, Blitzblau R, Bowen GM, Contreras CM, Daniels GA, Decker R, *et al*: Merkel cell carcinoma, version 1.2018, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 16: 742-774, 2018.
12. Shaikh WR, Sobanko JF, Etzkorn JR, Shin TM and Miller CJ: Utilization patterns and survival outcomes after wide local excision or mohs micrographic surgery for merkel cell carcinoma in the United States, 2004-2009. J Am Acad Dermatol 78: 175-177.e3, 2018.
13. Terushkin V, Brodland DG, Sharon DJ and Zitelli JA: Mohs surgery for early-stage Merkel cell carcinoma (MCC) achieves local control better than wide local excision +/- radiation therapy with no increase in MCC-specific death. Int J Dermatol 60: 1010-1012, 2021.
14. Yan L, Sun L, Guan Z, Wei S, Wang Y and Li P: Analysis of cutaneous merkel cell carcinoma outcomes after different surgical interventions. J Am Acad Dermatol 82: 1422-1434, 2020.
15. Schwartz JL, Wong SL, Mclean SA, Hayman JA, Lao CD, Kozlow JH, Malloy KM, Bradford CR, Frohm ML, Fullen DR, *et al*: NCCN guidelines implementation in the multidisciplinary Merkel cell carcinoma program at the university of Michigan. J Natl Compr Canc Netw 12: 434-441, 2014.
16. Tai P: A practical update of surgical management of merkel cell carcinoma of the skin. ISRN Surg 2013: 850797, 2013.
17. Dellambra E, Carbone ML, Ricci F, Ricci F, Di Pietro FR, Moretta G, Verkoskaia S, Feudi E, Failla CM, Abeni D and Fania L: Merkel cell carcinoma. Biomedicines 9: 718, 2021.
18. Singh B, Qureshi MM, Minh TT and Sahni D: Demographics and outcomes of stage I and II Merkel cell carcinoma treated with Mohs micrographic surgery compared with wide local excision in the National cancer database. J Am Acad Dermatol 79: 126-134.e3, 2018.
19. Lebbe C, Becker JC, Grob JJ, Malvehy J, Del Marmol V, Pehamberger H, Peris K, Saiag P, Middleton MR, Bastholt L, *et al*: Diagnosis and treatment of Merkel cell carcinoma. European consensus-based interdisciplinary guideline. Eur J Cancer 51: 2396-2403, 2015.
20. Kinas CG and Carroll BT: General guidelines for quality assurance of immunohistochemistry in a Mohs lab. Dermatol Surg 43: 507-511, 2017.
21. Hughes MP, Hardee ME, Cornelius LA, Hutchins LF, Becker JC and Gao L: Merkel cell carcinoma: Epidemiology, target, and therapy. Curr Dermatol Rep 3: 46-53, 2014.

22. Garza-Davila VF, Valdespino-Valdes J, Barrera FJ, Ocampo-Candiani J and Garza-Rodríguez V: Clinical impact of immunotherapy in Merkel cell carcinoma patients: A systematic review and meta-analysis. J Am Acad Dermatol 87: 121-130, 2022.
23. Lee AY and Berman RS: The landmark series: Non-melanoma skin cancers. Ann Surg Oncol 27: 22-27, 2020.
24. Nghiem P, Bhatia S, Lipson EJ, Sharfman WH, Kudchadkar RR, Brohl AS, Friedlander PA, Daud A, Kluger HM, Reddy SA, *et al*: Durable tumor regression and overall survival in patients with advanced Merkel cell carcinoma receiving pembrolizumab as first-line therapy. J Clin Oncol 37: 693-702, 2019.
25. D'Angelo SP, Bhatia S, Brohl AS, Hamid O, Mehnert JM, Terheyden P, Shih KC, Brownell I, Lebbé C, Lewis KD, *et al*: Avelumab in patients with previously treated metastatic Merkel cell carcinoma: Long-term data and biomarker analyses from the single-arm phase 2 JAVELIN Merkel 200 trial. J Immunother Cancer 8: e000674, 2020.
26. Topalian SL, Bhatia S, Amin A, Kudchadkar RR, Sharfman WH, Lebbé C, Delord JP, Dunn LA, Shinohara MM, Kulikauskas R, *et al*: Neoadjuvant nivolumab for patients with resectable merkel cell carcinoma in the checkmate 358 trial. J Clin Oncol 38: 2476-2487, 2020.