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CT-based qualitative classification of medication-related osteonecrosis of the jaw: association with surgical strategy and outcomes

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Article

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Abstract

Medication-related osteonecrosis of the jaw (MRONJ) exhibits marked heterogeneity in imaging appearance and clinical behavior, which is not fully captured by conventional staging systems. This retrospective observational study aimed to propose a novel computed tomography (CT)-based qualitative classification of MRONJ and to evaluate its clinical relevance in treatment selection and outcome prediction. A total of 253 patients diagnosed with MRONJ between 2014 and 2024 were analyzed. Based on CT findings, including osteolytic patterns, sequestrum separation, and periosteal reaction, lesions were classified into three types: type A (well-demarcated), type B (diffusely progressive), and type C (atypical). Associations between imaging classification, surgical procedures, and treatment outcomes were evaluated. Type A lesions were associated with favorable outcomes following limited surgery, whereas type B and type C lesions showed significantly poorer outcomes after conservative surgical approaches. Extended surgery resulted in comparable outcomes for type A and type B lesions, while type C lesions remained associated with unfavorable prognosis. These findings indicate that CT-based qualitative assessment reflects biologically relevant differences in MRONJ and may complement existing staging systems to optimize surgical decision-making and prognostic stratification.

Introduction

Medication-related osteonecrosis of the jaw (MRONJ) represents a significant complication arising from antiresorptive therapy, including bisphosphonates and denosumab, along with select anticancer and antiangiogenic medications. Following its initial documentation in 2003 [1], considerable investigative efforts have focused on understanding disease mechanisms and defining best-practice management approaches; despite this progress, consensus treatment protocols remain to be fully established [2, 3].

The American Association of Oral and Maxillofacial Surgeons (AAOMS) classification [4] serves as the predominant staging framework for MRONJ. This system stratifies disease as stage 1 (exposed bone without infection), stage 2 (exposed bone with infection), and stage 3 (extensive involvement of maxillary sinus or mandibular inferior border, or extraoral fistulation). While clinically practical for severity assessment and therapeutic guidance, this classification relies predominantly on disease extent rather than qualitative biological features or lesion heterogeneity.

In oncology, qualitative classifications based on biological characteristics, such as histological subtype and degree of differentiation, play a crucial role in determining treatment strategies and predicting prognosis, in addition to quantitative staging systems such as TNM. Similarly, in MRONJ, there is an increasing need for a novel evaluation framework that incorporates qualitative aspects of the lesion, including patterns of bone destruction, bone reactivity, and clarity of lesion margins, in addition to lesion extent and the presence of infection.

Progress in diagnostic imaging, notably computed tomography (CT), has facilitated comprehensive characterization of MRONJ lesion architecture and osseous response patterns [5]. Accumulating

evidence documents relationships between radiological features and clinical outcomes. Specifically, sequestrum formation, periosteal reaction subtypes [6–8], and mixed osteosclerotic alterations [9] have demonstrated prognostic value for surgical results and disease progression risk under conservative management. Moreover, certain subtypes characterized by extensive periosteal reaction despite minimal osteolysis [10], or by the absence of apparent osteolysis on CT [11, 12], have been associated with poor treatment outcomes.

These observations suggest that a systematic evaluation of imaging findings may enable the development of a classification system that more accurately reflects the qualitative characteristics of MRONJ lesions. Therefore, the aim of this study was to propose a novel CT-based qualitative classification of MRONJ and to evaluate its clinical utility, focusing on (1) its usefulness in treatment selection and (2) its contribution to prognostic prediction.

Materials and Methods

Study design and participants

This retrospective observational study included patients diagnosed with MRONJ who were treated at the Departments of Oral and Maxillofacial Surgery of Kansai Medical University Medical Center and Kansai Medical University Hospital between April 1, 2014, and March 31, 2024. MRONJ was diagnosed according to the AAOMS diagnostic criteria [2]. Patients with insufficient clinical records or CT images and those with a follow-up period of less than three months were excluded.
Ethical approval

This study was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan. Ethical approval was obtained from the Institutional Review Board of Kansai Medical University Hospital (approval number: 2022229). Owing to the retrospective nature of the study and the use of anonymized data, the requirement for informed consent was waived by the Institutional Review Board. Study information was disclosed on the hospital website, and an opt-out opportunity was provided in accordance with institutional guidelines.

Data collection and imaging evaluation

Data extraction from clinical records encompassed patient demographics (age, sex), underlying conditions, antiresorptive agent categories, radiological findings, and treatment outcomes. Two board-certified oral and maxillofacial surgeons performed blinded, independent CT image assessment. Discordant evaluations were resolved via consensus discussion.

The evaluated CT parameters included the presence of sequestrum separation, extent of osteolysis, and presence and type of periosteal reaction. The extent of osteolysis was classified as none, grade 1 (above the mandibular canal in the mandible or not reaching the maxillary sinus floor or nasal cavity floor), grade 2 (involving the mandibular canal or the maxillary sinus floor/nasal cavity floor), or grade 3

(resorption of the inferior mandibular border or extension beyond the maxilla to adjacent bones such as the zygomatic or sphenoid bones) (Fig. 1A). Periosteal reaction was classified as none, attached-type, gap-type, or irregular-type according to the classification proposed by Soutome et al. [7] (Fig. 1B).

Utilizing these radiological parameters, we established a three-category qualitative classification system (Fig. 1C): type A lesions exhibit distinct boundaries (well-demarcated pattern), type B lesions display indeterminate margins (diffusely progressive pattern), and type C lesions present atypical morphology. Type C includes specific subtypes, such as periosteal reaction–dominant type [10] and non-osteolytic type [11].

Treatment and outcome assessment

Surgical procedures were categorized as sequestrectomy, localized surgery (marginal mandibulectomy or partial maxillectomy), or extended surgery (segmental mandibulectomy or subtotal maxillectomy). Clinical outcome was defined as “healed” when all clinical symptoms, including bone exposure and fistula formation, had completely resolved; all other cases were classified as “non-healed”. Patients were followed for one year from the initial visit, and time to healing was recorded.

Statistical analysis

Statistical analyses were performed using SPSS version 26.0 (IBM Japan, Tokyo, Japan). Continuous variables were expressed as mean ± standard deviation, and categorical variables as number and percentage. Fisher’s exact test was used for categorical variables, and one-way ANOVA or the Kruskal–Wallis test for continuous variables, as appropriate. Time to healing was analyzed using Cox proportional hazards regression, and healing rates were estimated using the Kaplan–Meier method with comparisons by the log-rank test. A two-tailed p value < 0.05 was considered statistically significant.

Results

Patient characteristics

A total of 253 patients were included in the analysis, comprising 65 males and 188 females, with a mean age of 74.5 years. Low-dose ARAs were administered for osteoporosis in 123 patients, whereas high-dose ARAs were administered for bone metastases of malignant tumors in 130 patients. Regarding the type of ARA, 92 patients received bisphosphonates (BP), 131 received denosumab (DMB), and 30 were switched from BP to DMB. According to the proposed imaging classification, 94 patients were classified as type A, 118 as type B, and 41 as type C (Table 1).

Factors associated with imaging classification

Type A lesions were more frequently observed in patients with osteoporosis, whereas type B and type C lesions were more common in patients with malignant disease. Compared with BP-treated patients, those receiving DMB more frequently exhibited type B or type C lesions. Regarding periosteal reaction,

type A lesions were more often associated with no periosteal reaction or attached-type reaction, whereas gap-type and irregular-type reactions were more prevalent in type B and type C lesions (Table 2).

Treatment outcomes of all patients

The one-year healing rate was 83.8% among the 224 patients who underwent surgical treatment and 11.7% among the 29 patients treated conservatively, resulting in an overall healing rate of 76.4% for all 253 patients (Fig. 2). Because of the marked difference in outcomes, subsequent analyses were limited to the 224 surgically treated patients.

Factors associated with surgical procedures and outcomes

Among surgically treated patients, 42 underwent sequestrectomy, 134 underwent localized surgery, and 44 underwent extended surgery. Wide resection was more frequently performed in patients with malignant disease and in those with stage 3 MRONJ. The extent of osteolysis was significantly associated with the choice of surgical procedure; all patients with grade 3 osteolysis underwent extended surgery. However, wide resection was also performed in 32% of patients without osteolysis. Gap-type and irregular-type periosteal reactions were significantly associated with extended surgery (Table 3).

Despite differences in surgical invasiveness, the one-year healing rates did not significantly differ among sequestrectomy (81.2%), localized surgery (86.4%), and extended surgery (81.8%) (Fig. 3).

Prognostic factors according to surgical procedure

In both sequestrectomy and localized surgery, type A lesions showed significantly higher healing rates than type B or type C lesions. In contrast, after extended surgery, no significant difference in healing rates was observed between type A and type B lesions, whereas type C lesions remained associated with poor outcomes (Fig. 4).

Discussion

This investigation established a CT-derived qualitative categorization of MRONJ lesions (types A, B, and C) and examined its clinical applicability for surgical planning and outcome prediction. Our findings indicate that this classification framework yields clinically significant insights supplementing traditional staging approaches, especially for determining the appropriateness of conservative surgical interventions including sequestrectomy or marginal mandibulectomy/partial maxillectomy.

While the AAOMS classification represents the prevailing MRONJ assessment tool, its reliance on clinical manifestations and disease extent provides limited reflection of qualitative biological variation. Clinical experience demonstrates that lesions assigned identical stages frequently display divergent radiological phenotypes—ranging from circumscribed sequestrum formation to diffuse osteolytic

progression or prominent periosteal response with minimal osseous destruction. These observations suggest that MRONJ comprises heterogeneous disease entities rather than a single uniform condition.

Recent studies have emphasized the importance of CT findings in MRONJ. Periosteal reaction, particularly gap-type and irregular-type patterns, has been associated with poor surgical outcomes and a higher risk of recurrence, indicating that these areas should be considered in determining the resection margin [6–8]. Other reports have demonstrated that diffuse osteolytic changes or mixed osteosclerotic patterns are also associated with unfavorable outcomes [9]. Collectively, these findings support the concept that radiological features reflect underlying biological behavior and should be incorporated into treatment planning.

Based on these considerations, we classified MRONJ lesions according to CT features reflecting lesion quality: (1) type A, characterized by well-demarcated osteolysis with clear sequestrum formation; (2) type B, showing ill-defined and diffusely progressive osteolysis; and (3) type C, an atypical pattern including non-osteolytic lesions with dominant periosteal reaction. Using this classification, we identified distinct differences in treatment outcomes depending on both lesion type and surgical procedure.

Limited surgical approaches yielded excellent outcomes in type A lesions, suggesting that these cases are appropriate candidates for conservative surgical treatment. In contrast, type B and type C lesions showed significantly poorer outcomes following limited resection, indicating that reliance solely on lesion extent may lead to underestimation of disease spread and residual pathological bone.

Extended surgery resulted in comparable outcomes between type A and type B lesions, suggesting that more aggressive resection may compensate for the diffusely progressive nature of type B disease. However, type C lesions remained associated with unfavorable outcomes even after extended surgery, indicating that this subtype may represent a biologically distinct form of MRONJ that is less responsive to conventional surgical strategies.

One possible explanation for the persistently poor outcomes observed in type C lesions is profound suppression of bone turnover, particularly in patients receiving denosumab, resulting in impaired bone remodeling and poorly defined lesion margins. Such biological conditions may limit the formation of a clear demarcation between necrotic and viable bone, making complete surgical removal challenging even with extensive resection. Furthermore, the prominent periosteal reaction with minimal or absent osteolysis characteristic of type C lesions may serve as a surrogate marker of inflammatory spread beyond radiologically detectable bone destruction, leading to residual disease despite aggressive surgical intervention.

These findings suggest that treatment strategies for MRONJ should be determined not only by lesion extent but also by qualitative imaging characteristics that reflect underlying biological behavior. The proposed CT-based qualitative classification may complement existing staging systems by providing additional information for selecting appropriate surgical procedures, thereby avoiding both insufficient resection and unnecessary overtreatment.

This study has several limitations. First, its retrospective, single-center design and the limited number of surgeons involved may restrict generalizability. Second, the relationship between the proposed classification and outcomes of conservative (non-surgical) treatment was not fully evaluated. Despite these limitations, our results indicate that CT-based qualitative assessment provides clinically relevant information that may contribute to more individualized treatment strategies for MRONJ. Further multicenter prospective studies are warranted to validate this classification and to clarify its relationship with MRONJ pathophysiology.

Conclusion

This study proposes a novel CT-driven qualitative classification of MRONJ that reflects lesion heterogeneity and provides clinically meaningful information beyond conventional staging systems. The classification was significantly associated with surgical decision-making and treatment outcomes, particularly in patients undergoing limited surgical procedures. Incorporating qualitative imaging features into MRONJ assessment may enable more appropriate selection of surgical strategies and improve prognostic prediction. Further multicenter prospective studies are warranted to validate this classification and clarify its role in individualized MRONJ management.

Declarations

Ethical approval

Ethical approval

Competing Interests

The authors declare no competing interests.

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Author Contribution

Y.S. conceived and designed the study, collected and analyzed the data, and wrote the manuscript. S.S. contributed to data collection, imaging evaluation, and critical revision of the manuscript. Y.K. supervised the study, contributed to study design, data interpretation, and critical revision of the manuscript. All authors reviewed and approved the final manuscript.

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Data Availability

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

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Figures

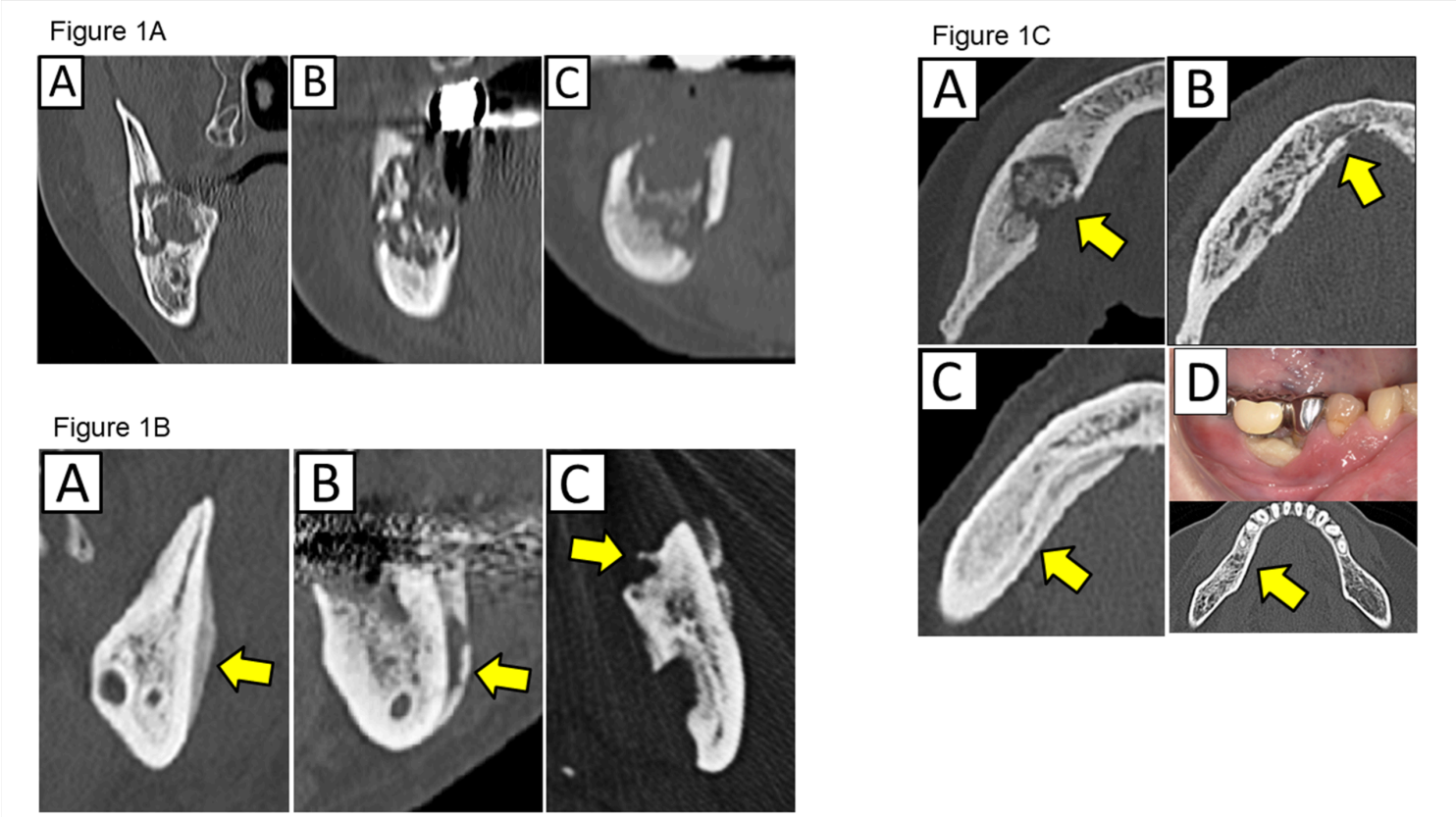


Figure 1

1A The extent of osteolysis

A: above the mandibular canal, B: involving the mandibular canal, C: extending to the inferior cortical bone.

1B Periosteal reaction

A: attached-type, B: gap-type, C: irregular-type.

1C A new CT-based classification of MRONJ

A: Type-A (well-demarcated type), B: Type-B (diffusely progressive type), C: Type-C (atypical type, periosteal-dominant type). D: Type-C (atypical type, non-osteolytic type).

Figure 2

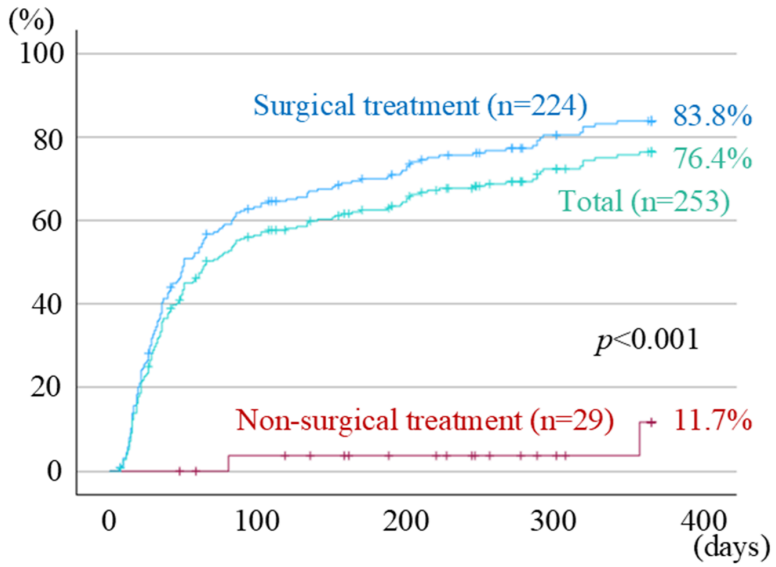


Figure 2

Cumulative healing rate in the surgical and non-surgical treatment groups

Good treatment outcomes were achieved in the surgical group, whereas the healing rate was low in the non-surgical group.

Figure 3

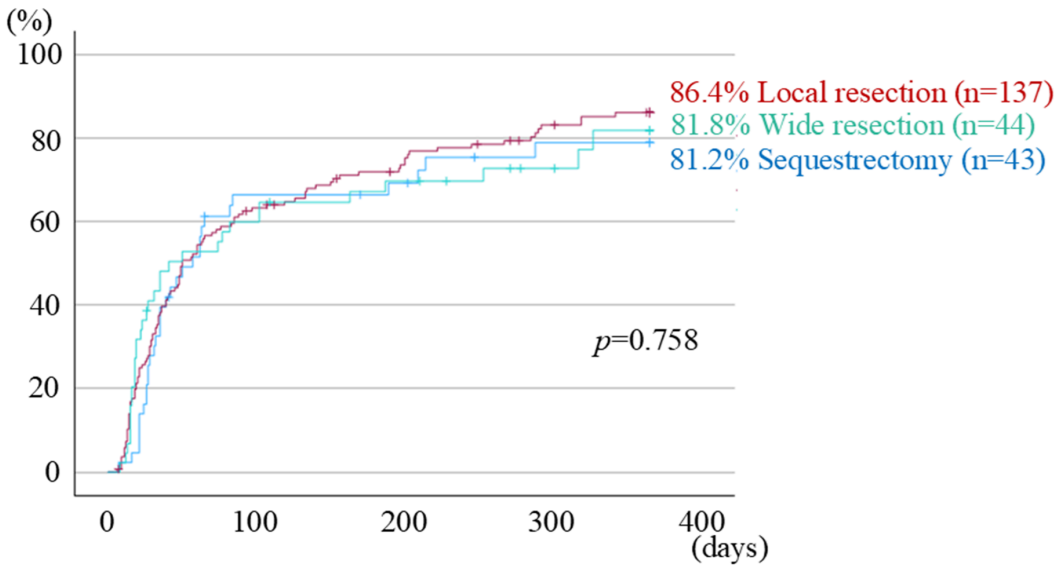


Figure 3

Treatment outcomes according to surgical procedure

No significant differences in healing rates were observed among sequestrectomy, localized surgery, and extended surgery.

Figure 4

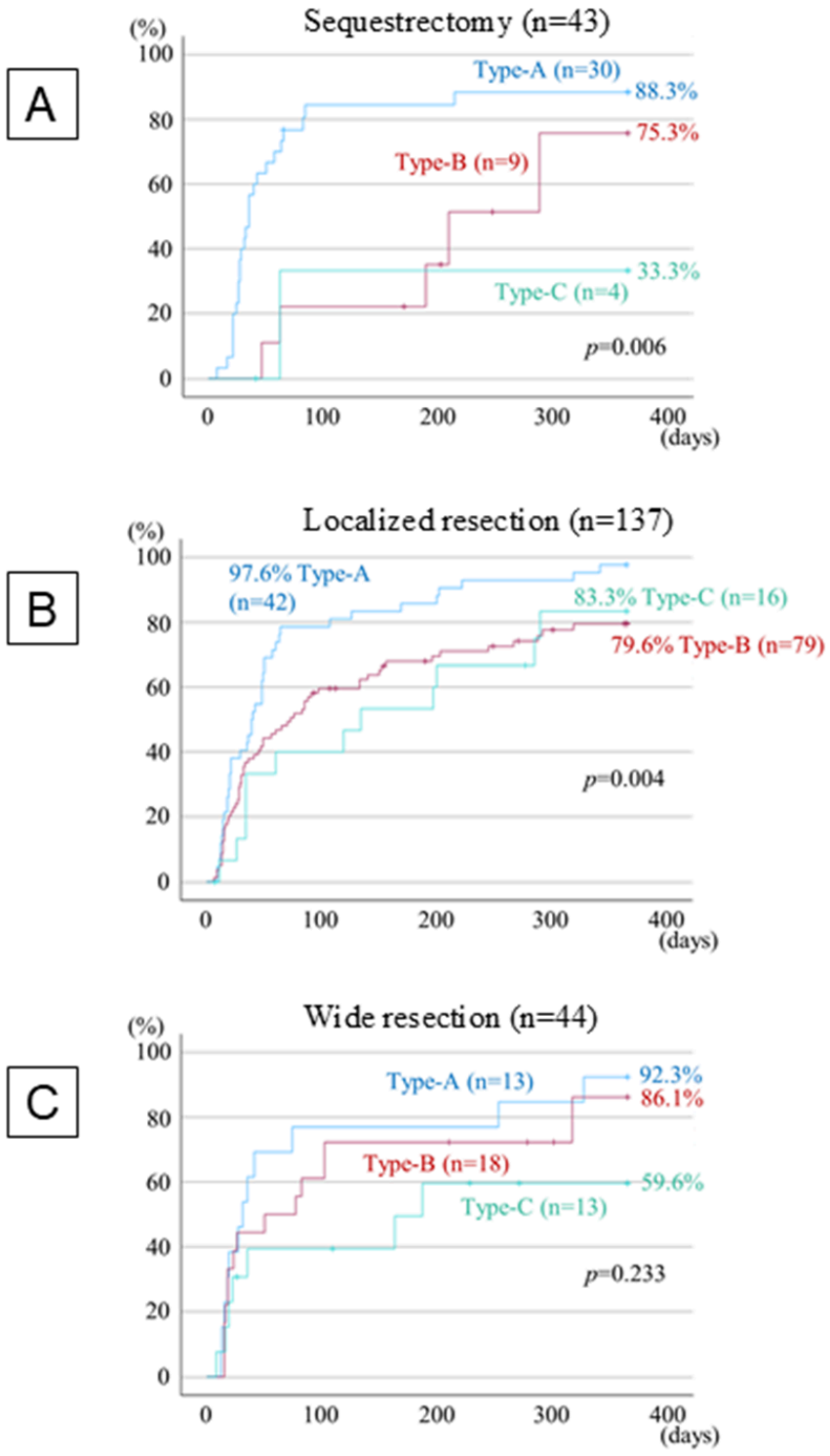


Figure 4

A new CT-based classification and treatment outcomes

In cases treated with sequestrectomy or localized resection, a significant association was observed between the new CT-based classification and treatment outcomes. In the extended surgery group, although no statistically significant difference was detected, type C tended to show poorer treatment outcomes.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table12.xlsx
- Table22.xlsx
- Table32.xlsx