The impact of COVID-19 pandemic on bone and soft tissue tumor treatment: a single institution study

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1 **The impact of COVID-19 pandemic on bone and soft tissue tumor**

2 **treatment: a single institution study**

3

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19 Abstract

20 Background: The spread of coronavirus disease 2019 (COVID-19) has caused
21 severe damage to routine medical care. This study aimed to investigate the
22 impact of COVID-19 on bone and soft tissue tumor treatment at a single
23 center.

24 Methods: A retrospective comparative study was conducted between two
25 groups of patients who received treatment at Osaka City University Hospital
26 during the peak of the COVID-19 pandemic (February-December 2020,
27 Group C) and during the same period the previous year (February to
28 December 2019, Group NC). Clinical data, including patient's age, sex,
29 tumor site, type of neoplasms, number of surgical cases for inpatients and
30 outpatients, operation time, use of implant, length of hospital stay, inpatient
31 hospitalization costs, number of inpatients receiving anticancer drugs, and
32 postoperative complications in these two groups were retrospectively
33 evaluated.

34 Results: The number of cases of malignant bone and soft tissue tumors that
35 were resected during hospitalization was predominantly higher in Group C
36 than in Group NC ($P=0.01$). There were no significant differences in

37 operation time, use of implant, and postoperative complications between
38 Groups C and NC; however, there were significant differences in the length
39 of hospital stay and hospitalization cost ($P<0.001$).

40 Conclusions: Globally, COVID-19 has affected several areas adversely. The
41 present study showed that the COVID-19 pandemic had an impact on the
42 hospitalization cost and length of hospital stay during the treatment of bone
43 and soft tissue tumor.

44

45 Keywords: COVID-19; coronavirus; bone and soft tissue tumor; pandemic;
46 surgery; hospitalization cost

47

48 **Introduction**

49 Several mysterious cases of pneumonia were reported for the first time in
50 Wuhan, China at the end of 2019. The causative agent was identified as
51 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the
52 disease was termed coronavirus disease 2019 (COVID-19) [1]. SARS-CoV-
53 2 belongs to a family of coronaviruses that have positive-sense single-
54 stranded RNA as their genome [2]. Coronavirus includes several species
55 that infect mammals and birds, but those that cause infections in humans are

56 the SARS coronavirus (SARS-CoV) and the Middle East respiratory
57 syndrome coronavirus (MERS-CoV), which cause severe pneumonia [2].
58 There are two possible routes of infection: droplet infection and contact
59 infection. It is extremely important to follow general infection control
60 measures, such as hand disinfection with alcohol and wearing a mask. The
61 incubation period for COVID-19 is reported by the World Health
62 Organization (WHO) as 1 to 12.5 days (mostly 5 to 6 days), and it is
63 recommended that suspected infected patients be monitored for 14 days [3].
64 Since 2019, the infections caused by SARS-CoV-2 has rapidly spread
65 worldwide, and the WHO declared COVID-19 as a global pandemic on
66 March 11, 2020 [4]. At present, the number of COVID-19 cases worldwide
67 has reached more than 300 million [5]. Economic losses because of COVID-
68 19 have been so great that various countries are providing economic support
69 measures to their population. In Japan, the government declared a state of
70 emergency on April 7, 2020 [6] along with implementing additional
71 economic stimulus measures to control the infection. The spread of COVID-
72 19 has caused severe damage to routine medical care, and there is a shortage
73 of medical personnel and hospital beds, resulting in the collapse of the
74 medical system.

75 Three vaccines have been shown to be effective against severe COVID-19:
76 AstraZeneca, Moderna, and Pfizer. Of these, Pfizer's coronavirus vaccine
77 was the first to be introduced in Japan [7]. The American pharmaceutical
78 giant Pfizer developed the vaccine in collaboration with BioNTech, a
79 German biotechnology company [8], and vaccinations began in the UK in
80 December 2020 [9]. In Japan, the vaccine was approved on February 12,
81 2021 and was administered to medical personnel, elderly people aged 65
82 years and older, and people with underlying diseases [10]. All the medical
83 staff in Japan completed Pfizer's vaccination program.

84 The COVID-19 pandemic has had a negative impact on many medical
85 fields [11-13]. For example, in cancer treatment, COVID-19 has led to
86 adjustments in treatments, such as anticancer drugs and immunotherapy, and
87 has caused delays or discontinuation of treatment [13]. In addition,
88 numerous other operations in various surgical fields have been cancelled or
89 postponed owing to the effects of COVID-19 [14]. However, to our
90 knowledge, no previous report has described the impact of COVID-19 on
91 bone and soft tissue tumor treatment. In this study, we investigated the
92 impact of COVID-19 on bone and soft tissue tumor treatment at our
93 hospital.

94

95 **Patients and Methods**

96 We conducted a retrospective comparative study between two groups of
97 patients who received treatment at Osaka City University Hospital during
98 the period of rapid spread of COVID-19 infections (February to December
99 2020, Group C) and during the same period of the previous year (February
100 to December 2019, Group NC). The inclusion criteria were outpatients and
101 inpatients who visited Osaka City University Hospital and patients treated
102 with anticancer drugs. Patients with incomplete medical records were
103 excluded from the study. The following items were examined: patient's age,
104 sex, site of tumor (bone or soft tissue), type of neoplasm (benign or
105 malignant), number of surgical cases (outpatient and inpatient surgery),
106 operation time, use of implant, length of hospital stay, inpatient
107 hospitalization cost, number of outpatients and inpatients, and number of
108 inpatients receiving anticancer drugs. In addition, perioperative
109 complications (soft tissue necrosis, pneumothorax, sepsis, wound infection,
110 and fracture) were recorded and defined as grade ≥ 3 based on the Common
111 Terminology Criteria for Adverse Events (CTCAE v5.0; National Cancer
112 Institute). For the anticancer treatment of malignant bone and soft tissue

113 tumors, we used a method similar to that reported by Hoshi et al. [15].
 114 Drugs for anticancer therapy for osteosarcoma included doxorubicin (DOX),
 115 cisplatin (CDDP), ifosfamide (IFM), and methotrexate (MTX). Drugs for
 116 anticancer therapy for Ewing's sarcoma included vincristine (VCR), DOX,
 117 and cyclophosphamide, alternating with IFM and etoposide (ETP) every 21
 118 days. Patients with high-grade soft tissue sarcomas received DOX- and
 119 IFM-based chemotherapy. Patients with metastatic soft tissue sarcomas
 120 received gemcitabine (GEM) and docetaxel (DTX). Patients who had soft
 121 tissue sarcomas refractory to, or who could not tolerate, anthracycline-based
 122 chemotherapy received trabectedin as second-line chemotherapy. Patients
 123 with advanced or metastatic soft tissue sarcomas received eribulin as
 124 second-line chemotherapy. For patients with relapse in the pulmonary or
 125 other sites, second-line chemotherapy comprised IFM, carboplatin, and ETP,
 126 with some modifications.

127 Anticancer drug-related adverse events (decreased neutrophil count, febrile
 128 neutropenia, decreased platelet count, pneumothorax, disseminated
 129 intravascular coagulation, pleural effusion, and heart failure) were also
 130 investigated and were defined as grade ≥ 3 based on the CTCAE.

131 This retrospective chart review study involving human participants was

132 conducted in accordance with the ethical standards of the Institutional and
133 National Research Committee and with the 1964 Helsinki Declaration and
134 its later amendments or comparable ethical standards. This comparative
135 retrospective study was approved by the institutional review board of our
136 institution.

137

138 Statistical Analysis

139 Fisher's exact probability test was performed to analyze categorical variables
140 (use of implant, anticancer drug-related adverse events, and postoperative
141 complications). The Mann-Whitney U test was used to compare various
142 clinical factors. Statistical significance was set at $P<0.05$. Statistical analysis
143 was performed using the Excel Statistics software for Windows (version
144 2020; SSRI Co., Ltd., Tokyo, Japan).

145

146 **Results**

147 Clinical characteristics of the two groups

148 Table 1 shows a comparison of the clinical characteristics of Groups C and
149 NC for inpatients. Of the 253 patients treated for bone and soft tissue tumors,
150 114 (45%) were in Group C while 139 (55%) were in Group NC. The patients'

151 mean age in Groups C and NC was 57 ± 21 years and 55 ± 22 years, respectively.
 152 Group C had 66 (58%) men while Group NC had 78 (56%) men. The tumor
 153 origin site was the bone in 44 cases in Group C and in 59 cases in Group NC.
 154 The tumor origin site was soft tissue in 70 cases in Group C and in 80 cases
 155 in Group NC. Histologically malignant cases were found in 57 and in 50 cases
 156 in Groups C and NC, respectively. Histologically benign cases were found in
 157 57 and in 89 cases in Groups C and NC, respectively. The number of cases of
 158 malignant bone and soft tissue tumors resected during hospitalization was
 159 predominantly higher in Group C than in Group NC ($P=0.01$). The median
 160 (range) operation time was 70 min (42–138 min) and 56 min (33–97 min) in
 161 Groups C and NC, respectively ($P=0.2$). Sixteen patients underwent surgery
 162 with implants in Groups C and NC ($P=0.3$). Postoperative complications,
 163 such as soft tissue necrosis, wound infection, pneumothorax, and fracture,
 164 were observed in eight patients in Group C and in four patients in Group NC
 165 ($P=0.15$). There were no significant differences in operation time, use of
 166 implant, and postoperative complications between Groups C and NC. The
 167 median (range) length of hospital stay was 12 days (8–23 days) in Group C
 168 and 8 days (5–16 days) in Group NC. The median (range) hospitalization cost
 169 was USD 8497 (USD 4733–13845) and USD 5305 (USD 3598–9197) in

170 Groups C and NC, respectively. There were significant differences in the
171 median length of hospital stay and median hospitalization cost between
172 Groups C and NC ($P<0.001$).

173 Table 2 shows a comparison of the clinical characteristics of Group C vs.
174 Group NC for day surgery and chemotherapy. The number of days of surgery
175 was 16 days in Group C and 26 days in Group NC. We surveyed the number
176 of patients who visited the outpatient clinics of orthopedic surgeons engaged
177 in bone and soft tissue tumor care at our hospital. Table 3 shows a comparison
178 of the number of outpatients during the COVID-19 pandemic vs. the non-
179 COVID-19 era. The total number of outpatients who visited the outpatient
180 clinics of bone and soft tissue oncologists was 2429 and 2548 patients in
181 Groups C and NC, respectively. The increase in the number of COVID-
182 positive patients by month had little impact on the number of outpatients in
183 2020.

184 In this study, we administered various anticancer drugs to patients, with
185 ADR, IFM, and trabectedin being the most common. A decrease in the
186 neutrophil count was the most common type of anticancer drug-related
187 adverse event. There were significant differences in the anticancer drug-
188 related adverse events between Groups C and NC ($P=0.03$).

189 In orthopedic surgery, implants are often used, and surgery is performed in
190 the presence of a vendor. However, because of the COVID-19 outbreak,
191 vendors have been prohibited in the operating room at our hospital to reduce
192 the number of people in the operating room as much as possible and to prevent
193 the spread of COVID-19. Therefore, our hospital switched to online
194 attendance in orthopedic surgery by adopting remote work. Figure 1 shows a
195 left femur bone tumor with curettage and plate fixation using Compression
196 Hip Screw surgery performed through the use of a tablet which allowed the
197 staff to communicate with each other, and helped in identifying errors in the
198 implant insertion procedure and other processes. Through this technique, it is
199 also possible to immediately respond to complications during surgery.
200 However, in addition to the difficulty of direct explanation and guidance from
201 the vendor online, orthopedic surgery is a complex procedure that involves
202 the use of multiple surgical instruments; thus, the surgeon and the operating
203 nurse must also be familiar with the implant.

204

205 **Discussion**

206 The global COVID-19 pandemic has had a profound negative impact on
207 the healthcare industry [11]. In addition to the shortage of medical supplies

208 [16], hospital beds [12], and personnel [17], it has also affected the field of
209 surgery and caused postponement of scheduled surgeries [14].

210 In this study, the number of inpatient and outpatient surgeries showed a
211 downward trend compared to the non-COVID-19 era, but the number of
212 surgeries for malignant bone and soft tissue tumors for inpatients remained
213 the same as in the previous year. In our hospital, surgeries for malignant
214 bone and soft tissue tumors have been actively performed. The French
215 Sarcoma group mentions that it is not recommended to delay surgery for
216 operable patients without COVID-19 symptoms, particularly for grade 2 or
217 3 soft tissue sarcomas [18]. Surgical treatment of the primary tumor is
218 inevitable for the treatment of malignant bone and soft tissue tumors. These
219 tumors grow at a rapid rate, and the larger the tumor, the more difficult it is
220 to resect, making local control of the tumor difficult. Regardless of the
221 histologic grade, the prognosis for locally recurrent tumors is poor.
222 Therefore, early surgical treatment is necessary for patients without specific
223 COVID-19 symptoms and should take precedence over surgery for
224 degenerative diseases.

225 Previous reports on the association between anticancer drugs and COVID-
226 19 have speculated that people receiving systemic anticancer therapy have a

227 higher risk of death from COVID-19, especially in hematological
228 malignancies, but no significant differences were reported in the solid tumor
229 group [19]. In this study, there were significant differences in the anticancer
230 drug-related adverse events between Groups C and NC ($P=0.03$). However,
231 COVID-19 may have been unlikely to be associated with anticancer drug-
232 related adverse events because of the large number of anticancer drugs used
233 in this study and the variety of patient backgrounds.

234 All patients admitted to the hospital underwent a polymerase chain reaction
235 (PCR) test prior to admission, and in principle, patients were admitted after
236 confirming that the PCR test was negative. As a countermeasure against
237 fever in hospitalized patients undergoing anticancer drug treatment, all
238 patients with fever were placed in a private room. Physicians were equipped
239 with personal protective equipment and underwent PCR testing. If the
240 patient PCR test results were negative, the possibility of febrile neutropenia
241 was suspected, and various culture tests were performed. Antibiotics were
242 administered empirically. If the PCR test was positive, the patient was
243 diagnosed with COVID-19, and the patient's general condition was carefully
244 monitored with continued private room management.

245 In this study, the median (range) length of hospital stay was 12 days (8–23

246 days) in Group C and 8 days (5–16 days) in Group NC. The median (range)
 247 hospitalization costs were USD 8497 (USD 4733–13845) and 5305 (USD
 248 3598–9197) in Groups C and NC, respectively. There were significant
 249 differences in the median length of hospital stay and median hospitalization
 250 cost between Groups C and NC ($P<0.001$). The COVID-19 pandemic has
 251 forced hospitals to undertake various preventive measures. At our hospital,
 252 PCR tests are performed on the day of admission or 2 days prior to surgery
 253 for patients scheduled for surgery, and negative results are confirmed. If
 254 necessary, a chest computed tomography (CT) scan is also performed to
 255 check for pneumonia. These measures may have contributed to the increase
 256 in the length of hospital stay and rising cost of medical care.

257 Japan has become a super-aged society, with the elderly population
 258 accounting for 28.9% of the total population, which is a record high. This
 259 indicates that one of every four people in Japan is aged 65 years or older
 260 [20]. Consequently, medical costs have been rising, and it is necessary to
 261 reduce the medical costs in the future. However, the COVID-19 outbreak
 262 has caused a large loss to the Japanese economy because of the high medical
 263 costs.

264 In this study, we investigated the impact of the COVID-19 pandemic on bone

265 and soft tissue tumor treatment. There was no change in the number of
266 inpatient surgeries for malignant bone and soft tissue tumors, the number of
267 surgeries for benign tumors decreased, and there was no change in the number
268 of surgeries for outpatients. The addition of tests, such as PCR and
269 preoperative chest CT, at the time of hospitalization may lead to longer
270 hospital stays and higher medical costs. In addition, the number of outpatients
271 did not fluctuate according to the number of COVID-19 cases.

272 We conducted a survey on the impact of COVID-19 on bone and soft tissue
273 tumor care and found that it had an impact on the cost of medical care but had
274 no impact on the number of surgeries for malignant bone and soft tissue
275 tumors. COVID-19 has caused a collapse in healthcare systems, including a
276 shortage of medical resources, medical personnel, and hospital beds.
277 Furthermore, it has had an impact on the hospitalization cost and the length
278 of hospital stay for patients undergoing treatment for bone and soft tissue
279 tumors.

280

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283

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286

287 **Ethical approval:**

288 Study approval was obtained from the institution, and all investigations were

289 conducted in accordance with the ethical principles of research.

290

291 **Patient consent for publication:**

292 The patients provided consent for the publication of patient data.

293

294 **Competing interests:**

295 The authors have no conflicts of interest to declare.

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303 **Table captions**

304 Table 1. Comparison of inpatient clinical information during the SARS-CoV-

305 2 era (Group C) and during the non-SARS-CoV-2 (Group NC) era.

Table 1. Comparison of inpatient clinical information during the SARS-CoV-2 era (Group C) and during the non-SARS-CoV-2 (Group NC) era.

Characteristics	Group C N=114	Group NC N=139	P value
Median age (years)	57(7-92)	55(5-88)	0.7
Gender			
Male	66	78	0.4
Female	48	61	
Type of tumor			
Bone	44	59	0.3
Soft tissue	70	80	
Neoplasms			
Malignant	57	50	0.01
Benign	57	89	
Operation time (min)	70(13-351)	56(15-515)	0.2
Use of Implant			
Yes	16	16	0.3
No	98	123	
Postoperative complications(CTCAE v5.0)			
Soft tissue necrosis	8	4	0.15
Pneumothorax	5	2	
Sepsis	1		
Wound infection	1	1	
Fracture		1	
Median length of hospital stay (days)	12(2-89)	8(2-117)	<0.001
Hospital cost(US dollars)	8,497	5,305	<0.001

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316 Table 2. Comparison of clinical information during the SARS-CoV-2 era

317 (Group C) and during the non-SARS-CoV-2 (Group NC) era for day surgery

318 and chemotherapy.

Table 2. Comparison of clinical information during the SARS-CoV-2 era (Group C) and during the non-SARS-CoV-2 (Group NC) era for day surgery and chemotherapy.

Characteristics	Group C	Group NC	P value
Day surgery	16	26	0.4
Malignant	3	3	
Benign	13	23	
Chemotherapy	90	64	0.03
DOX, IFM	18	14	
DOX	3	3	
IFM	4	6	
Trabectedin	21	12	
IE	12	7	
VDC	13	6	
DOX CDDP	11	1	
ICE	4	2	
MTX	2	4	
GEM DTX	1	6	
Eribulin	1	3	
Anticancer drug-related adverse events	14	20	
Neutrophil count decreased	10	13	
Febrile neutropenia	2	2	
Platelet count decreased	1	2	
Pneumothorax		1	
Disseminated intravascular coagulation		1	
Pleural effusion		1	
Heart failure	1		

DOX doxorubicin; IFM ifosfamide; VDC vincristine and cyclophosphamide and actinomycin-D;

CDDP cisplatin; ICE ifosfamide and cisplatin and etoposide; MTX methotrexate; GEM gemcitabine

DTX docetaxel

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329 Table.3 Comparison of the number of outpatients during the SARS-CoV-2 era

330 (Group C) and during the non-SARS-CoV-2 (Group NC) era.

Table 3. Comparison of the number of outpatients during the SARS-CoV-2 era (Group C) and during the non-SARS-CoV-2 (Group NC) era.

Month	Group C N=2429	Group NC N=2548	Number of new PCR positive patients in 2020	P value
January	223	323	1	
February	173	205	0	
March	254	253	14	
April	208	188	257	
May	122	182	282	
June	204	188	36	
July	263	262	125	
August	201	196	1537	
September	200	145	624	
October	205	213	619	
November	169	176	603	
December	207	217	2014	
Total	2429	2548		0.9

331

332 **Figure captions**

333 Figure 1. A vendor attending a surgery online.

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