creative commons
COMMONS DEED

저작자표시-비영리-변경금지 2.0 대한민국

이용자는 아래의 조건을 따르는 경우에 한하여 자유롭게

- 이 저작물을 복제, 배포, 전송, 전시, 공연 및 방송할 수 있습니다.

다음과 같은 조건을 따라야 합니다:

저작자표시. 귀하는 원저작자를 표시하여야 합니다.

비영리. 귀하는 이 저작물을 영리 목적으로 이용할 수 없습니다.

변경금지. 귀하는 이 저작물을 개작, 변형 또는 가공할 수 없습니다.

- 귀하는, 이 저작물의 재이용이나 배포의 경우, 이 저작물에 적용된 이용허락조건을 명확하게 나타내어야 합니다.
- 저작권자로부터 별도의 허가를 받으면 이러한 조건들은 적용되지 않습니다.

저작권법에 따른 이용자의 권리는 위의 내용에 의하여 영향을 받지 않습니다.

이것은 이용허락규약(Legal Code)을 이해하기 쉽게 요약한 것입니다.

Disclaimer

dCollection

의학석사 학위논문

Surgery for Bone Metastases in Lung Cancer: Does the Use of Targeted Agents Change the Outcome?

폐암의 골 전이에 대한 수술적 치료의 결과: 표적항암제 도입에 따른 영향 분석

2022년 2월

서울대학교 대학원

의학과 정형외과학 전공

양 은 규

Surgery for Bone Metastases in Lung Cancer: Does the Use of Targeted Agents Change the Outcome?

지도교수 한 일 규

이 논문을 의학석사 학위논문으로 제출함
2021년 10월

서울대학교 대학원
의학과 정형외과학 전공
양 은 규

양은규의 석사 학위논문을 인준함
2022년 1월

위 원 장 김 학 재 (인)

부위원장 한 일 규 (인)

위 원 김 한 수 (인)

Abstract

Surgery for Bone Metastases in Lung Cancer: Does the Use of Targeted Agents Change the Outcome?

Eunkyu Yang

Department of Medicine (Major in Orthopedic Surgery)

The Graduate School

Seoul National University

The introduction of targeted agents, which targets specific biological pathways with less toxicity and greater potency than cytotoxic chemotherapeutic agents, has improved survival of patients with advanced cancer. However, few studies have been published on outcome of bone metastases surgery who received targeted therapy. Therefore, this study sought to assess the post-operative survival, local tumor control and non-oncological complications in patients who received targeted therapy compared to the cytotoxic chemotherapy.

Patients (n=74) who underwent surgery for bone metastasis to the extremities and pelvis from lung cancer were reviewed. Patients who received either cytotoxic chemotherapy (n=29) or targeted agent (n=45) were included. Patients were classified as responders (stable disease or better) or non-responders based on the RECIST criteria. We also classified the patients based on the operation type, en bloc resection group and curettage group. We compared postoperative survival after the surgery for metastatic bone lesion, local recurrence rate at the site of bone metastasis, and non-oncological complication rate among the classified groups. The Kaplan-Meier method and the Cox proportional hazard regression were used to analyze the postoperative survival. The chi-square test, the Fisher's exact test, and the logistic regression were used to analyze the local recurrence rate and the non-oncological complication rate.

Overall, patients who received targeted agents had significantly longer postoperative survival than patients with cytotoxic chemotherapy (24.7 ± 3.9 months vs. 15.7 ± 4.8 months, P=0.003) on Kaplan-Meier analysis. Patients with better response to therapeutic agents showed significantly longer postoperative survival, both in the cytotoxic group (32.1 ± 9.8 months vs. 4.2 ± 0.7 months, P=0.003) and in the targeted group (35.1 ± 5.5 months vs. 9.3 ± 2.0 months, P<0.001). Cox proportional hazards regression analysis showed that the type of chemotherapy and patient's response to the agent were significantly associated with the postoperative survival.
In terms of local recurrence rate and non-oncological rate, there was no statistically significant result comparing each subgroup. However, despite the lack of statistical significance, we could find out several important findings in our data.

Local recurrence rate was slightly higher in cytotoxic group than in targeted group. (17.2% (5/29) vs. 11.1% (5/45), P=0.451) Non-oncological complication rate was higher in patients with targeted agent than in those with cytotoxic agent. (17.8% (8/45) vs. 6.9% (2/29), P=0.181) Among patients who received targeted agents, non-oncological complication rate was higher in responders than in non-responders. (25% (7/28) vs. 5.9% (1/17), P=0.104) Logistic regression analysis showed that there were no significant factors associated with the local recurrence and the non-oncological complication, respectively.
There were 4 patients who underwent re-operations. Re-operation rate was higher in targeted therapy group than in cytotoxic chemotherapy group. The rate was higher in curettage group than in en bloc resection group.

The primary objective of this study was to investigate the change of treatment in metastatic bone tumor patients after the introduction of targeted agents. We expected that patients who used targeted agents would live longer than patients who used cytotoxic chemotherapeutic agents, and also expected that local recurrence rate and non-oncological complication rate can be therefore higher in targeted therapy group because of the survival gain. Our findings partly correspond with our hypothesis; there was survival gain in the patients who used targeted agents, especially with good response. In addition, the local recurrence rate and non-oncological complication rate tended to be slightly higher in the subgroups which showed longer survival. However, our findings should be interpreted cautiously, since part of our data lacks statistical significance due to the small study population in each group.

In conclusion, targeted agents improved post-operative survival in patients undergoing surgery for bone metastases. In the era of targeted therapy, selection of surgical options that provide durable stabilization is required, especially for patients responding to targeted agents. Furthermore, the statistical model for predicting the prognosis of metastatic bone cancer patients could be addressed in further studies.

keywords : Targeted therapy, Lung cancer, Bone metastasis, RECIST criteria

Student Number **: 2020-25910**

Contents

List of Tables

List of Figures

Introduction

Bone metastasis is one of considerable factors causing significant morbidity, reduction in quality of life, and functional loss in solid tumor patients, even shortening life expectancy. [1] About 30-40% of lung cancer patients and 20-25% of renal cell carcinoma patients develop skeletal metastasis during the course of disease. [2] Therefore, managing metastatic bone cancer patients has been a major concern of physicians who deal with solid organ cancers. Furthermore, because metastatic destruction of bone might cause pathologic fractures in long bones and epidural expansion in spine that result in main disabilities of patients [2], reducing the tumor burden of bone metastasis has been a main interest of orthopedic tumor surgeons.

The introduction of targeted agents, which target specific biological pathways with less toxicity and greater potency than cytotoxic chemotherapeutic agents, has improved survival of patients with advanced cancer. For example, lung cancer patients who received treatment with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) had a much longer median overall survival than patients who did not receive EGFR TKIs. (24 months vs. 11 months) [3] In addition, renal cell carcinoma patients treated with nivolumab, one of targeted agents, had a survival gain compared with patients treated with everolimus. (25.0 months vs. 19.6 months) [4]

To our knowledge, there was just one article published on outcome of bone metastases surgery in the era of targeted agent, which deals with local recurrence, implant survival, and postoperative survival rate of metastatic bone cancer patients. [5] This study reveals that

targeted therapy improves the overall longevity of metastatic bone cancer patients, but there was no statistical difference in implant survival and local recurrence.

Considering the potency of targeted agents proven by previous studies, we hypothesized that metastatic bone cancer patients using targeted agents can expect longer survival compared to the patients using conventional cytotoxic chemotherapeutic agents. Also, we also hypothesized that because of longer survival, the chance for local recurrence of cancer and non-oncological complication could be increased in the era of targeted agents.

Therefore, the aim of this study was to assess the postoperative survival, local tumor control and non-oncological complications in patients who received targeted therapy compared to the conventional cytotoxic chemotherapy.

Methods

Patients selection

This retrospective cohort study was approved by our institutional review board. We collected data from patients who had undergone orthopedic tumor surgeries for bone metastases in our institution from February 2006 to March 2019. Because both targeted therapy and cytotoxic chemotherapy are commonly used in the treatment of lung cancer, which was the most frequent cancer in our data, we included lung cancer patients in this study. We excluded patients who did not take on any chemotherapeutic agent (n=3); and patients who discontinued follow-up to our institution. (n=14) When one patient underwent several surgeries for multiple bone metastases, we analyzed only the first orthopedic tumor surgery in this study. On the basis of these criteria, 74 patients were included, 45 in targeted group and 29 in cytotoxic group (Fig. 1). We reviewed medical charts, X-ray radiographs, CT scans, MRI images, and bone scan images of the patients during analysis.

Patients characteristics

For demographic analysis of study population, patients' sex, age at cancer diagnosis, and interval from cancer diagnosis to bone metastasis were retrieved. Thirty-nine patients (52.7%) were men in our study data, seventeen (37.8%) in targeted group, and twenty-two (75.9%) in cytotoxic group. The mean age at cancer diagnosis was 59.82 ± 11.23 years, and the mean interval from cancer diagnosis to bone metastasis was 1.94 ± 2.18 years (Table 1). The mean

follow-up period of entire population was 13.9 months (range, 1-73 months), and the mean follow-up period of survived patients was 27.5 months (range, 3-73 months).

In terms of the treatment of the bone metastasis, location of tumor, type of resection, type of reconstruction, and administration of perioperative radiation therapy were investigated. The most frequently involved bone of metastatic cancer was femur; forty-five patients (60.8%).

Surgery for bone metastasis was done for impending or existing pathologic fractures. All surgeries were performed by two senior orthopedic oncologists (H-S Kim and I Han). Surgical treatment was composed of two main procedures; (1) resection of tumor and (2) reconstruction of resected bone. The type of resection was either en-bloc resection or curettage. En-bloc resection was defined as resecting the metastatic lesion as a whole surrounded with normal tissue, and curettage was defined as removing grossly visible tumors under direct vision in surgical field. The type of reconstruction was categorized into three groups; (1) Endoprosthesis (2) Internal fixation and (3) No metal reconstruction. Patients who underwent surgeries using prosthetic implant to replace original joint were defined as "Endoprosthesis" group. Patients who underwent surgeries using metal implant for internally fixating bone, not using prosthetic implant were defined as "Internal fixation" group. Patients who underwent surgeries not using any metal implant, just resecting the bone tumor or performing cement augmentation to the bone were defined as "No metal reconstruction" group. Timing of surgical intervention and surgical options regarding resection and reconstruction were determined by (1) patients' symptom; (2) patients' performance status and expected survival; (3) location of main lesion in the metastatic

bone; (4) response to chemotherapy or radiation therapy before surgery; and (5) preference of surgeon and patient. Twenty-two patients (29.7%) had undergone en-bloc resection, and the most used method for reconstruction was internal fixation; forty-three patients (58.1%).

The administration of perioperative radiation therapy was determined by orthopedic oncologists according to each patient's status considering upon the possibility of local recurrence, after discussing with medical oncologists and radiation oncologists. Twenty patients (27.0%) had undergone preoperative radiation therapy for the metastatic lesion. Twenty-five patients (33.8%) had undergone the radiation therapy postoperatively.

In addition, each patient's data for the histologic type of cancer and mutational profile was retrieved from the pathology report. The most frequent histologic type was adenocarcinoma; twenty patients (69.0%) in cytotoxic group and thirty-five patients (77.8%) in targeted group. Thirty patients (66.7%) in targeted group and nine patients (31.0%) in cytotoxic group had identified mutation.

Postoperative surveillance follow-up was performed at 2 weeks and then 3-6 month intervals, with imaging such as plain radiographs, MRI scans, CT scans, or bone scans. The schedule and imaging modality depended upon each patient's postoperative condition.

Chemotherapy

We divided our patients into two groups; (1) cytotoxic group; and (2) targeted group. If the patient received targeted chemotherapeutic agent at any time during his or her entire treatment course, he or she was included in targeted group (although the targeted agent was used for second or third line treatment). The patient who only used

conventional cytotoxic chemotherapeutic agent and had not been treated with any targeted agent during his or her entire treatment course was classified as cytotoxic group. There were twenty-nine patients (39.2%) in cytotoxic group; and forty-five patients (60.8%) in targeted group.

We considered the response of tumor burden to the chemotherapy can have influence on our result, we classified our patients by RECIST (Response Evaluation Criteria in Solid Tumors). There are 4 categories in RECIST; 1) Complete Response (CR) 2) Partial Response (PR) 3) Stable Disease (SD) 4) Progressive Disease (PD). [6] As medical oncologists document the RECIST criteria of all patients undergoing chemotherapy in our institution, we grouped the patients using the medical documentation. Because multiple chemotherapeutic agents were used in one patient and the response can differ among each other agents, we investigated the best response based on RECIST within his or her entire treatment period in each patient, whether before or after surgery. Patients were then classified as responders (stable disease or better) or non-responders based on the RECIST. Twelve patients (41.4%) of cytotoxic group and twenty-eight patients (62.2%) of targeted group showed response to chemotherapy.

In our study, tyrosine kinase inhibitors (i.e. erlotinib, gefitinib, crizotinib, alectinib, afatinib, osimertinib), monoclonal antibody therapy (i.e. nivolumab, cemiplimab), mTOR (mechanistic target of rapamycin) inhibitors (i.e. temsirolimus, everolimus), and immunotherapic agent (i.e. anti PD-L1 agent, anti PD-1 agent, interferon alpha) were classified as targeted chemotherapeutic agents.

We investigated the targeted agent which showed the best response in RECIST throughout the patient's entire treatment period. If more

than two agents showed the same best response in a patient, we regarded the agent which was used for longer period as the agent with best response. In our study group, gefitinib was the most frequent agent which showed the best response (n=19), followed by crizotinib (n=7), erlotinib (n=7) and nivolumab (n=4).

Endpoints

After classifying the subjects, we analyzed postoperative survival, local recurrence (LR) rate, and non-oncological complication rate in each divided group. LR was defined as radiological identification of recurrence in the operated tumor bed. [7] We used plain radiographs, CT scans, MR images, bone scan images for the radiologic identification. Non-oncological complication was defined as complication in the operated tumor bed except local recurrence, which included metal breakage, implant loosening, dislocation of prosthesis, postoperative infection, periprosthetic fracture, nonunion and malunion of fracture, heterotopic ossification, and avascular necrosis of femoral head. Complications other than postoperative infection were regarded upon radiological image findings, including plain radiographs, CT scans, and MR images. Postoperative infection was defined as the situation like (1) pus-like discharge at the operated wound; (2) redness, swelling at the operated wound; (3) abnormal laboratory findings (i.e. elevated CRP, elevated ESR) which cannot be explained except infection at operated bed; (4) wound dehiscence at the operated wound; in which the patient needed additional antibiotics treatment and/or surgical treatment. Lastly, we figured out all the re-operation cases in our patient data.

Statistical analysis

We presented continuous variables as a mean with SD (standard deviation) and categorical variables as frequencies with percentages during the statistical analysis.

Postoperative survival and LR-free survival were estimated using Kaplan-Meier survival curves and the log-rank test for comparison. To clarify the strength of associations between various factors and the postoperative survival, univariate Cox proportional hazards regression was performed for each variable. To eliminate confounding bias among the variables, multivariate Cox proportional hazards regression was performed using the variables with P values of <0.1 in univariate analysis.

Local recurrence rate and non-oncological complication rate in each group were statistically analyzed by the chi-square test and the Fisher's exact test. Univariate and multivariate logistic regression were performed to find out possible associations.

A P-value of less than 0.05 was considered to indicate statistical significance. Statistical analyses were performed using the SPSS software (Version 25.0; IBM Co., Armonk, NY).

Results

Postoperative survival

In all, 54 of 74 patients (73.0%) died during the follow-up, and the postoperative survival rate calculated via Kaplan-Meier method at 6 months, 1 year, and 2 years, 4 years was 62.0%, 37.2%, 30.1%, 15.7%, respectively.

The mean overall postoperative survival was 21.1 months (range, 1-73 months). Patients who received targeted agents had significantly longer postoperative survival than patients who received cytotoxic chemotherapy (24.7 ± 3.9 months vs. 15.7 ± 4.8 months, P=0.003) (Fig. 2A). Patients classified as responders (stable disease or better in RECIST criteria) had significantly longer postoperative survival than patients classified as non-responders, both in the cytotoxic chemotherapy group (32.1 ± 9.8 months vs. 4.2 ± 0.7 months, P=0.003) and in the targeted therapy group (35.1 ± 5.5 months vs. 9.3 ± 2.0 months, P<0.001). There was no significant difference in survival between the responders in the cytotoxic chemotherapy group and the responders in the targeted therapy group (P=0.254) (Fig. 2B). However, in the non-responders, the targeted therapy group has significantly longer post-operative survival (9.3 ± 2.0 months vs. 4.2 ± 0.7 months, P=0.003) (Fig. 2C).

According to multivariate Cox proportional hazards regression, cytotoxic group (HR=2.460, P=0.004, compared to targeted therapy) and non-responder group (HR=3.624, P<0.001, compared to responder) showed independent associations with shorter postoperative survival. (Table 2) None of the factors related to patient demographics, type of

reconstruction, extent of tumor resection, perioperative radiotherapy, histologic type of cancer, and mutational status were associated with postoperative survival.

Local recurrence

Ten patients (14%) developed local recurrence(LR) after a mean time of 6.8 months (range, 1-18 months). The incidence of LR was higher in the cytotoxic group than in the targeted group although there was no significant significance (17.2% (5/29) vs. 11.1% (5/45), P=0.451). On Kaplan-Meier analysis, the cytotoxic group showed a tendency toward shorter LR-free survival than the targeted group (53.7 ± 7.9 months vs. 55.7 ± 4.8 months, P=0.098) (Fig. 3). Of note, the rate of en bloc resection was higher in the cytotoxic group (Table 1). Among the responders, the incidence of LR was higher in the cytotoxic group than in the targeted group although there was no significant significance (16.7% (2/12) vs. 7.1% (2/28), P=0.394). However, in the non-responders, the LR incidence was similar between the two groups (17.6% (3/17) vs. 17.6% (3/17), P=1.000). Responders showed a tendency toward a lower incidence of LR than non-responders in targeted group (7.1% (2/28) vs. 17.6% (3/17), P=0.277), but there was no significant difference in the incidence of LR between responders and non-responders in cytotoxic group (16.7% (2/12) vs. 17.6% (3/17), P=0.945).

The univariate logistic regression showed that type of reconstruction in surgery can have association with local recurrence. Compared to “no metal reconstruction” group, “internal fixation” group (HR=0.132, P=0.017) and “endoprosthesis” group (HR=0.045, P=0.013) had lower risk for local recurrence. (Table 3) However, the other factors showed no association with local recurrence.

Non-oncological complications

Ten patients (14%) developed non-oncological complications related surgery after a mean time of 7.7 months (range, 1-25 months). The complication rate was higher in the targeted group than in the cytotoxic group although there was no significant significance (17.8% (8/45) vs. 6.9% (2/29), P=0.181). In the targeted group, the responders showed a tendency toward a higher complication rate than non-responders (25% (7/28) vs. 5.9% (1/17), P=0.104). The most common complication was heterotopic ossification in the targeted group and postoperative infection in the cytotoxic group.

The univariate logistic regression showed that none of the factors related to patient demographics, type of chemotherapy, response to chemotherapy, type of reconstruction, extent of tumor resection, perioperative radiotherapy, histologic type of cancer, and mutational status were associated with postoperative survival. (Table 4)

Re-operation

There were four patients who underwent re-operations. Re-operation rate was higher in targeted group than in cytotoxic group. (6.7% (3/45) vs. 3.4% (1/29), P=0.550) The rate was higher in curettage group than in en bloc resection group. (5.8% (3/52) vs. 4.5% (1/22), P=0.831) (Table 5)

Discussion and Conclusion

The primary objective of this study was to investigate the change of treatment and prognosis of metastatic bone tumor patients after the introduction of targeted agents. Although it was proved by previous researches that targeted agents contribute to the survival gain of patients with advanced cancers, [3][4] as far as our knowledge, there was no previous study especially dealing with metastatic bone cancer patients. We regarded the postoperative survival, local recurrence rate, and non-oncological complication rate as the primary endpoints of this study, and focused on the difference of data between the targeted group and the cytotoxic group. Furthermore, we classified the patients in each group by response to the chemotherapy, type of resection, type of reconstruction, administration of perioperative radiation therapy, and investigated whether these factors had influence on the treatment and prognosis.

The estimation of postoperative survival is a considerable factor when deciding the extent of tumor resection and the method of surgical treatment for metastatic bone cancer patients. [8][9] In a recent study, a statistical model, PATHFx model, for predicting life expectancy of metastatic bone cancer patients by preoperative status was suggested. In this model, ten prognostic features, including (1) age at the time of surgery (2) sex (3) indication for surgery (impending or completed pathologic fracture) (4) number of bone metastases (solitary or multiple) (5) surgeon's estimate of survival (postoperatively, in months) (6) presence or absence of visceral metastases (7) presence or absence of lymph node metastases (8)

preoperative hemoglobin concentration (9) absolute lymphocyte count and (10) the patient's primary oncologic diagnosis were parameters to estimate the postoperative survival of patients. [10]

Our study showed that the postoperative survival was longer in the targeted group than in the cytotoxic group. Especially we classified our patients according to the best response to the chemotherapy along the entire treatment period, and the patients with better response lived longer than the patients with worse response. The difference was larger in the targeted group. Using our result, we believed that the response to chemotherapy could be a critical factor in the statistical model to predict postoperative survival of metastatic bone cancer patients which can be used preoperatively.

However, there is a considerable limitation to apply our result directly to the model. We retrospectively investigated the best response to the chemotherapeutic agent along the entire treatment period of each patient, so some patients showed the best response to the agent used postoperatively, and the other patients showed the best response to the agent used preoperatively. Expectation of survival duration is made before the operation in order to decide a proper surgical treatment. Therefore, if we intend to include the response to chemotherapy as a factor in the prediction model, we need to collect the data about the response to the preoperative agent only. We believe that this topic can be addressed in future studies.

In terms of local recurrence rate and non-oncological complication rate, there was no statistically significant result comparing each subgroup. However, despite the lack of statistical significance, we could find out several important findings in our data.

In patients with metastatic bone cancer, durable surgical stabilization can provide lifelong pain relief and functional recovery.

[11] Local recurrence of tumor can affect the durability of stabilization, and can eventually lead to re-operation of patients. [12][13] According to our team's previous study, [7] the surgical margin and the primary cancer type have effect on the local recurrence after surgery, but the type of chemotherapy was not investigated. Therefore, we intended to find out whether the introduction of targeted agent made change to the local recurrence rate of metastatic bone cancer patients in this study.

The local recurrence rate was higher in the curettage group than in en bloc resection group. This result coincides with previous studies. Patients with en bloc resection had a significantly lower incidence of local recurrence than patients who underwent curettage in our team's previous study. [7]

Furthermore, in our study, among patients in targeted group, the local recurrence rate was higher when the patients underwent radiotherapy to the operation field preoperatively or postoperatively. This result is controversial to the previous studies and conventional common concepts that radiotherapy can reduce local recurrence rate of metastatic bone cancer patients. [14][15] Because our study is not a matched comparative study and our result lacks statistical significance, the correlation of local recurrence rate and radiotherapy in metastatic bone cancer patients in targeted therapy era should be studied more deeply and could be revealed in future studies.

Non-oncological complications such as infection, prosthesis dislocation, metal loosening, metal failure, and heterotopic ossifications can also have effect on the durability of surgical stabilization in metastatic bone cancer patients. Oncologic patients are fragile to surgical complications as proved in previous studies. In a study, a rate of infectious complication ranges from 1.2% to 19.5% [14]. Such

complications can have a great impact on patients' quality of life and functional recovery after surgery. [8] We planned to compare the complication rate in targeted group to the rate in cytotoxic group.

The non-oncological complication rate was higher in targeted group than in cytotoxic group. The complication rate was higher in patients who had response to the therapy than who did not have any response to the therapy in targeted group. This situation can happen due to the elongation of survival of patients. The patients with longer survival might have more chance to confront complications.

However, if the targeted agents make the histological environment more fragile to surgical complications including infection, this can also contribute to the increase in the non-oncological complication rate. Therefore, further study is needed to find out the reason why non-oncological complication rate is higher in targeted therapy group.

The non-oncological complication rate was higher in curettage group than in en bloc resection group. This results coincides with the previous study. [16] We assumed that remnant cancer cells can have influence on the stability of metal implants, and can make the operative field more vulnerable to postoperative infection due to the lack of immunity.

In addition, our results shows that non-oncological complication rate was higher in patients who received radiotherapy preoperatively or postoperatively than in patients who did not undergo any radiotherapy. According to the previous study, [14] one of the most important factors related to the infection risk is preoperative radiotherapy. Radiation can make tissue necrotic and fragile with damaged blood vessels. It can also make chronic ischemia of soft tissue, and reduce immunity of the tissue. [17] Therefore, radiotherapy can contribute to the increase in non-oncological

complication rate.

There were four re-operation cases in our whole study population. Patients in the targeted group had higher re-operation rate than patients in the cytotoxic group. Patients who underwent curettage are more likely to confront the re-operation than those who underwent en bloc resection. This coincides with the result that both the local recurrence rate and the non-oncological complication rate were higher in those groups, as described above.

In addition to the endpoint of our study, there were several statistical tendencies from our data.

In terms of the gender of patients, the proportion of female was larger in the targeted group (28/45, 62.2%) than in the cytotoxic group (7/29, 24.1%). Gefitinib, crizotinib and erlotinib were most frequently used targeted chemotherapeutic agents in our study. According to previous studies, gefitinib and erlotinib target epidermal growth factor receptor (EGFR) of lung adenocarcinoma cells [18] [19]. Crizotinib targets multiple tyrosine kinases including anaplastic lymphoma kinase (ALK) kinase [20]. Because echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) translocation causes lung adenocarcinoma [21], crizotinib can suppress the growth of cancer cells targeting ALK kinase. In previous studies, the genetic mutations of lung adenocarcinoma were identified at higher frequencies in females than in males. [22] This can support the higher proportion of females in the targeted group.

Furthermore, the duration between diagnosis of primary cancer and diagnosis of bone metastasis was longer in the targeted group (2.139 ± 2.072 years) than in the cytotoxic group (1.638 ± 2.342 years) (P=0.338). This can be explained by the difference in (1) potency of

disease activity and (2) potency of chemotherapy.

As described above, most targeted agents used in lung cancer are applied to lung adenocarcinoma patients. The proportion of adenocarcinoma patients is larger in the targeted group, and the proportion of squamous cell carcinoma and small cell lung cancer patients is larger in the cytotoxic group. As the disease activity of squamous cell carcinoma and small cell lung cancer is more potent than adenocarcinoma in lung cancer [23][24][25], the duration between diagnosis of primary cancer and diagnosis of bone metastasis can differ in the targeted group and the cytotoxic group.

The difference of interval from cancer diagnosis to bone metastasis can be also made by the difference in potency of chemotherapy. In concordance with previous studies [3][4], postoperative survival was longer in the targeted group than in the cytotoxic group in our study data. We can postulate that targeted agents are more potent than cytotoxic agents in terms of suppressing the growth of cancer cells. Therefore, the interval from cancer diagnosis to bone metastasis between the two groups can be different.

There were several limitations to our study. First, because the study was a non-randomized and retrospective study, it has a potential to have selection bias. In deciding appropriate chemotherapeutic agents, medical oncologists may consider the patient's physiological and functional status. Because targeted therapy can impose financial burden to cancer patients, the patients who are too sick to undergo targeted therapy may not be offered the treatment by physicians, and there are strict criteria to select patients who undergo the targeted therapy. This selection could make bias to our survival analysis. Future randomized controlled trials would further clarify the change caused by the introduction of targeted

therapeutic agents.

Also, our study has small sample size and low incidence of events. We divided our patients by type of chemotherapy, response to the treatment, type of surgery, whether they underwent the radiotherapy, histologic type, and mutational status. After dividing, the size of subgroups were too small and this made the comparison among each subgroups more difficult. Our finding lacked statistical significance, and the result should be interpreted with caution. Future studies with more samples can have statistical power and elucidate the difference of local recurrence rate and non-oncological complication rate more clearly than this study.

As far as our knowledge, this study was the first study which investigated the treatment of metastatic bone cancer patients in depth after the introduction of targeted chemotherapeutic agents.

There was survival gain in patients who used targeted chemotherapeutic agents, compared to patients who used cytotoxic chemotherapeutic agents. Especially, the postoperative survival was longer in those who showed better response to chemotherapy. On the basis of our result, we suggest that we should consider the type of chemotherapeutic agent and patient's response to chemotherapy together for the estimation of postoperative life expectancy of the patient, when deciding the surgical treatment plan preoperatively.

Furthermore, according to our result, the local recurrence rate and non-oncological complication rate were higher in groups which showed longer postoperative survival.

In further studies, the statistical model for predicting the life expectancy of metastatic bone cancer patients preoperatively could be addressed, applying the result of our study.

References

1. Berenson J., Rajdev L., Broder M. (2006) Managing bone complications of solid tumors. Cancer BiolTher 5: 1086 - 1089.
2. Coleman R. (2001) Metastatic bone disease: clinical features, pathophysiology and treatment strategies. Cancer Treat Rev 27: 165 - 176.
3. H-M Bae et al. (2012) Prognostic factors for non-small cell lung cancer with bone metastasis at the time of diagnosis. Lung cancer 77: 572-577.
4. R.J. Motzer et al. (2015) Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med 373: 1803-13.
5. C.J. Gutowski et al. (2019) Should the Use of Biologic Agents in Patients With Renal and Lung Cancer Affect Our Surgical Management of Femoral Metastases. Clin Orthop Relat Res 477: 707-714.
6. Eisenhauer EA et al. (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45(2): 228-47.
7. Krishnan CK et al (2017) Factors associated with local recurrence after surgery for bone metastasis to the extremities. J Surg Oncol. 2017;1 - 8.
8. Wedin R, Bauer HC (2005) Surgical treatment of skeletal metastatic lesions of the proximal femur: endoprosthesis or reconstruction nail? J Bone Joint Surg Br. 87: 1653 - 7.
9. Quinn R et al. (2014) Contemporary management of metastatic bone disease: tips and tools of the trade for general practitioners. Instr Course Lect. 63: 431 - 41.

10. Piccioli A et al. (2015) How do we estimate survival? External validation of a tool for survival estimation in patients with metastatic bone disease – decision analysis and comparison of three international patient populmations. BMC Cancer 15: 424.
11. Damron TA, Sim FH. (2000) Surgical treatment for metastatic disease of the pelvis and the proximal end of the femur. Instr Course Lect. 49:461 – 470.
12. Miller BJ, Soni EE, Gibbs CP, Scarborough MT. (2011) Intramedullary nails for long bone metastases: why do they fail? Orthopedics. 34:274.
13. Wedin R, Bauer HC, Wersall P. (1999) Failures after operation for skeletal metastatic lesions of long bones. Clin Orthop Relat Res. 358:128 – 139.
14. Guzik G (2018) Oncological and functional results after surgical treatment of bone metastases at the proximal femur. BMC Surgery 18:5.
15. Pergolizzi S, Pontoriero A, Delia P, Santacaterina A. (2004) External beam irradiation in the palliation of bone metastases : a practice analysis among Sicilian departments of radiation oncology. Tumori. 90:86 – 90.
16. Chan D, Carter SR, Grimer RJ, Sneath RS (1992) Endoprosthetic replacement for bony metastases. Ann R Coll Surg Engl. 74(1): 13-18.
17. Ashford RU, Hanna SA, Park DH, Pollock RC, Skinner JA, Briggs TW, Cannon SR. (2010) Proximal femoral replacements for metastatic bone disease: financial implications for sarcoma units. Int Orthop. 34:709 – 13.
18. Armour AA, Watkins CL (2010) The challenge of targeting EGFR: experience with gefitinib in nonsmall cell lung cancer. Eur

Respir Rev. 19(117): 186-96.
19. Costa DB et al. (2008) Effects of erlotinib in EGFR mutated non-small cell lung cancers with resistance to gefitinib. Clin Cancer Res 14(21): 7060-7067.
20. Kwak EL et al. (2010) Anaplatic Lymphoma Kinase Inhibition in Non-Small-Cell Lung Cancer. N Engl J Med 363: 1693-1703.
21. Inamura K et al. (2015) EML4-ALK Fusion Is Linked to Histological Characteristics in a Subset of Lung Cancers. J Thorac Oncol. 3(1) : 13-17.
22. Mazieres J et al. (2013) Speecificities of Lung Adenocarcinoma in Women Who Have Never Smoked. J Thorac Oncol. 8: 923-929.
23. Wang BY et al. (2020) The Comparsion Between Adenocarcinoma and Squamous Cell Carcinoma in Lung Cancer Patients. J Cancer Res Clin Oncol. 146(1): 43-52.
24. Cooke DT et al. (2010) Survival Comparison of Adenosquamous, Squamous Cell, and Adenocarcinoma of the Lung After Lobectomy. Ann Thorac Surg. 90: 943-8.
25. Kawase A et al. (2011) Differences Between Squamous Cell Carcinoma and Adenocarcinoma of the Lung: Are Adenocarcinoma and Squamous Cell Carcinoma Prognostically Equal? Jpn J Clin Oncol 42(3): 189-195.

Table 1.
Characteristics of patients

	Cytotoxic group (n=29)	Targeted group (n=45)	P-value
Sex			0.001
Female	7	28	
Male	22	17	
Age at cancer diagnosis (mean ± SD)	62.34 ± 9.994	58.20 ± 11.776	0.122
Interval from cancer diagnosis to bone metastasis (mean ± SD, years)	1.638 ± 2.342	2.139 ± 2.072	0.338
Response by RECIST			0.079
Responder			
Complete response	0	0	
Partial response	6	20	
Stable disease	6	8	
Non-responder			
Progressive disease	17	17	
Peri-operative radiotherapy			
Done			0.974
Pre-operative only	8	8	
Post-operative only	7	14	
Pre- & post-operative	1	3	
Not done	13	20	
Resection			0.215
En bloc	11	11	
Curettage	18	34	
Reconstruction			0.052
Endoprosthesis	10	13	
Internal fixation	13	30	
No metal	6	2	

	Cytotoxic group (n=29)	Targeted group (n=45)	P-value
Histologic type			0.280
Non-small cell lung cancer	26	44	
Adenocarcinoma	20	35	
Squamous cell carcinoma	6	7	
Unclassified	0	2	
Small cell lung cancer	2	0	
Others*	1	1	
Mutational status			0.004
Mutation identified	9 †	30 ‡	
EGFR	1	21	
ALK	1	7	
KRAS	2	0	
BRAF	1	0	
C-MET	2	3	
HER-2	2	1	
TP53	3	1	
Unidentified	20	15	
Location			
Femur	15	30	
Pelvic bone	5	1	
(Acetabulum)	(1)	(0)	
(Pubis)	(1)	(0)	
(Ilium)	(3)	(1)	
Tibia	1	2	
Fibula	0	1	
Calcaneus	1	0	
Humerus	5	11	
Scapula	1	0	
Ulna	1	0	

* There were 2 patients whose tumor cells showed neuroendocrine differentiation
† 2 patients had multiple mutated genes ; 1 with C-MET and HER-2 ; and 1 with KRAS and HER-2
‡ 3 patients had multiple mutated genes ; 1 with EGFR and C-MET ; 1 with C-MET and HER-2 ; and 1 with EGFR and TP53

Table 2.

Univariate and multivariate Cox proportional hazards regression for postoperative survival

	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	P-value	Hazard ratio	95% CI	P-value
Age at cancer diagnosis (years)	1.009	(0.983 - 1.035)	0.509			
Interval from cancer diagnosis to bone metastasis (years)	0.878	(0.760 - 1.016)	0.080	0.940	(0.812 - 1.089)	0.412
Chemotherapy						
Targeted group	1.00 (Reference)			1.00 (Reference)		
Cytotoxic group	2.156	(1.248 - 3.724)	0.006	2.460	(1.336 - 4.528)	0.004
Response to chemotherapy (RECIST)						
Responder	1.00 (Reference)			1.00 (Reference)		
Non-responder	4.238	(2.340 - 7.676)	<0.001	3.624	(1.948 - 6.743)	<0.001
Reconstruction						
No metal reconstruction	1.00 (Reference)					
Internal fixation	0.994	(0.414 - 2.385)	0.989			

Endoprosthesis	0.668	(0.255 - 1.750)	0.412			
Extent of tumor resection						
En bloc resection	1.00 (Reference)			1.00 (Reference)		
Curettage	1.769	(0.930 - 3.364)	0.082	1.712	(0.833 - 3.517)	0.143
Perioperative radiotherapy						
Done	1.00 (Reference)					
Not done	0.765	(0.441 - 1.325)	0.339			
Histology						
Adenocarcinoma	1.00 (Reference)					
Squamous cell carcinoma	1.928	(0.960 - 3.874)	0.065			
Small cell lung cancer	0.473	(0.064 - 3.471)	0.461			
Others	-	-	0.969			
Mutational status						
Mutation identified	1.00 (Reference)					
Mutation unidentified	1.092	(0.636 - 1.874)	0.75			

Table 3.

Univariate and multivariate logistic regression for local recurrence

	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value
Age at cancer diagnosis (years)	0.970	(0.913 - 1.031)	0.330			
Interval from cancer diagnosis to bone metastasis (years)	0.330	(0.099 - 1.101)	0.071	0.400	(0.114 - 1.405)	0.153
Chemotherapy						
Targeted group	1.00 (Reference)					
Cytotoxic group	1.667	(0.437 - 6.358)	0.455			
Response to chemotherapy (RECIST)						
Responder	1.00 (Reference)					
Non-responder	0.519	(0.133 - 2.016)	0.343			
Reconstruction						
No metal reconstruction	1.00 (Reference)					
Internal fixation	0.132	(0.025 - 0.699)	0.017	0.193	(0.035 - 1.067)	0.059

Endoprosthesis	0.045	(0.004 – 0.520)	0.013	0.085	(0.007 – 1.027)	0.053
Extent of tumor resection						
En bloc resection	1.00 (Reference)					
Curettage	0.985	(0.230 – 4.221)	0.984			
Perioperative radiotherapy						
Done	1.00 (Reference)					
Not done	1.286	(0.339 – 4.883)	0.712			
Histology						
Adenocarcinoma	1.00 (Reference)					
Squamous cell carcinoma	1.068	(0.199 – 5.748)	0.939			
Small cell lung cancer	–	–	0.999			
Others	–	–	0.999			
Mutational status						
Mutation identified	1.00 (Reference)					
Mutation unidentified	1.133	(0.299 – 4.299)	0.854			

Table 4.
Univariate logistic regression for non-oncological complication

	Univariate analysis		
	Odds ratio	95% CI	P-value
Age at cancer diagnosis (years)	1.021	(0.961 - 1.085)	0.509
Interval from cancer diagnosis to bone metastasis (years)	0.905	(0.624 - 1.312)	0.598
Chemotherapy			
Targeted group		1.00 (Reference)	
Cytotoxic group	0.343	(0.067 - 1.743)	0.197
Response to chemotherapy (RECIST)			
Responder		1.00 (Reference)	
Non-responder	0.456	(0.108 - 1.923)	0.285
Reconstruction			
No metal reconstruction		1.00 (Reference)	
Internal fixation	-	-	0.999

Endoprosthesis	-	-	0.999
Extent of tumor resection			
En bloc resection		1.00 (Reference)	
Curettage	0.985	(0.230 - 4.221)	0.984
Perioperative radiotherapy			
Done		1.00 (Reference)	
Not done	0.266	(0.052 - 1.352)	0.110
Histology			
Adenocarcinoma		1.00 (Reference)	
Squamous cell carcinoma	1.247	(0.227 - 6.842)	0.800
Small cell lung cancer	-	-	0.999
Others	2.286	(0.258 - 25.147)	0.499
Mutational status			
Mutation identified		1.00 (Reference)	
Mutation unidentified	1.133	(0.299 - 4.299)	0.854

Table 5. Summary of 4 patients who underwent re-operation

Sex / Age	Chemo therapy	RECIST	Reason for re-operation	Time to re-operation	Operated bone	Surgical margin	Radiation therapy
F/70	Targeted	PR	Periprosthetic fracture	25 months	Humerus	Curettage	Done
F/69	Targeted	PR	Malunion and aseptic loosening of implant	24 months	Humerus	Curettage	Done
F/41	Targeted	PR	Infection	25 months	Femur	En bloc	Done
F/45	Cytotoxic	PD	Infection	3 months	Pelvic bone	Curettage	Done

Figure 1. Flowchart of the study population

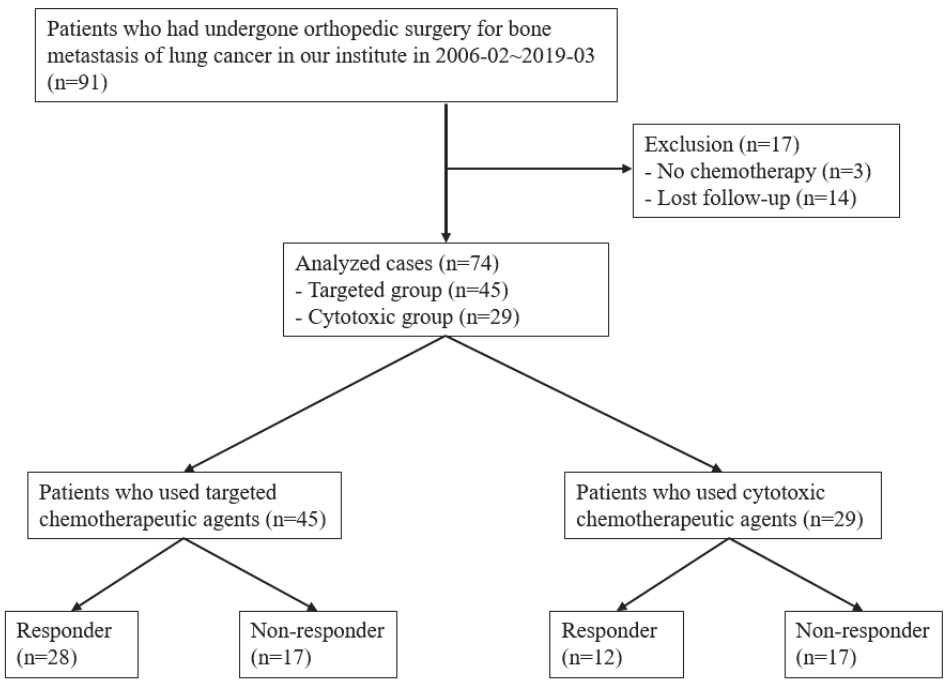
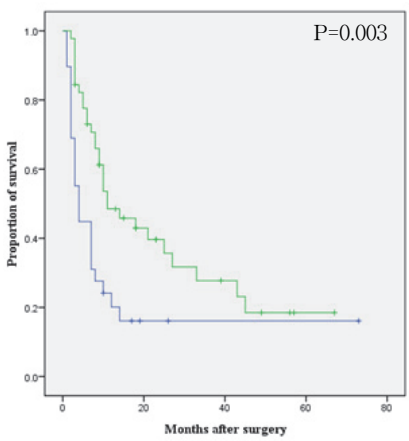


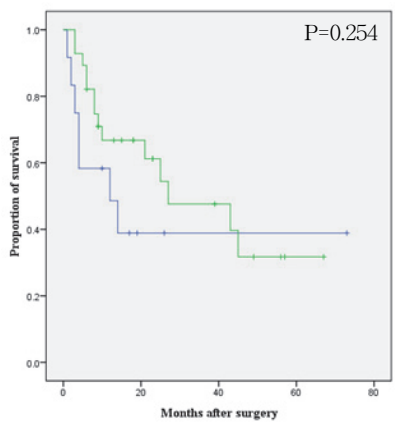
Figure 2.
Postoperative survival analyses

comparing targeted therapy group (green) and conventional cytotoxic chemotherapy group (blue)
(A) in total (B) in responders (C) in non-responders

(A)



(B)



(C)

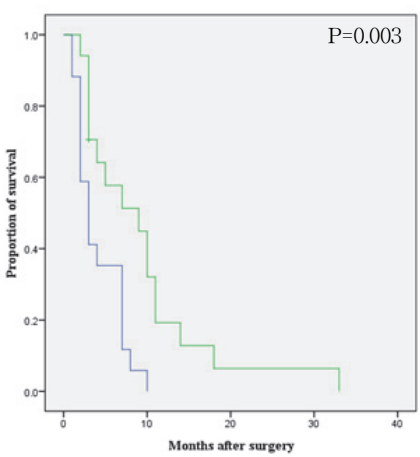
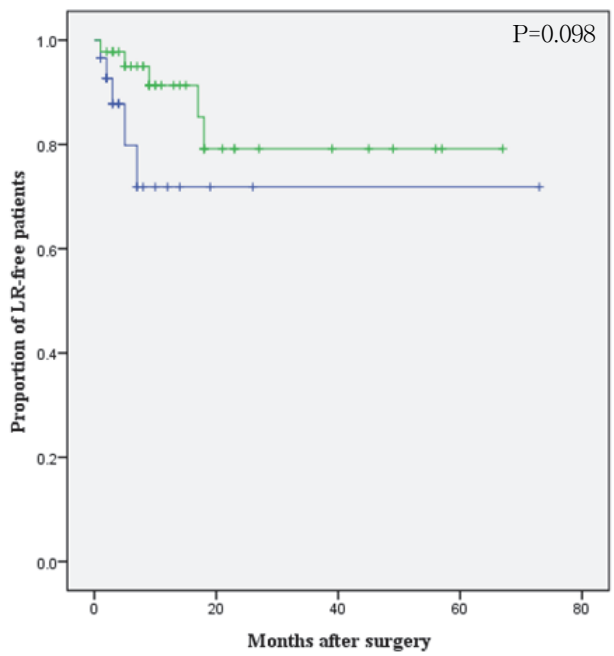


Figure 3.
Postoperative local recurrence-free survival analyses

comparing targeted therapy group (green) and conventional cytotoxic chemotherapy group (blue) in lung cancer patients



국 문 초 록

폐암의 골 전이에 대한 수술적 치료의 결과: 표적항암제 도입에 따른 영향 분석

양 은 규
의학과 정형외과학 전공
서울대학교 대학원

표적항암제란 세포 내 특정 생물학적 신호전달체계를 표적으로 하여 작용하는 항암제로, 기존의 세포독성항암제에 비하여 약물의 독성은 적고, 세포사멸 효과는 강력한 특징을 지닌다. 이러한 표적항암제의 도입 이후, 진행된 암 환자들의 생존 기간이 크게 향상되었다. 그러나 표적항암제 치료를 받은 골전이암 수술 환자들의 치료 결과를 다룬 연구는 그동안 진행된 바가 많지 않았다. 따라서 이번 연구를 통하여, 골전이암 환자들에게 있어서 세포독성항암치료와 비교하여 표적항암치료를 받았을 때에 수술 후 생존 기간, 국소적인 종양의 재발 및 수술 관련 합병증 등에 어떠한 차이가 있는지 살펴보았다.

폐암의 상, 하지 골전이로 인하여 치료를 받은 74명의 환자의 치료 결과를 살펴보았다. 이 중 45명의 환자는 표적항암치료를 진행하였고, 29명의 환자는 세포독성항암치료만을 진행하였다. 환자들을 RECIST 기준에 따라 항암 치료에 반응한 군과 반응하지 않은 군으로 분류하였으며, 수술 전 후 방사선 치료 여부 및 수술 중

종양의 절제연, 종양의 돌연변이 유무, 종양의 병리학적 특징에 따라 추가적으로 환자군을 분류하였다. 골전이에 대한 수술 후 환자들의 생존 기간, 수술 부위 국소 재발률 및 수술 관련 합병증 발생률을 각 군 별로 비교하였다. 생존 기간 분석을 위해서는 Kaplan-Meier 방법 및 Cox 회귀 분석을 사용하였고, 국소재발률 및 합병증 발생률을 비교하기 위하여 카이제곱검정 및 Fisher의 정확성 검정, 로지스틱 회귀 분석을 이용하여 통계 분석을 진행하였다.

표적항암치료를 받은 폐암 환자들이 세포독성항암치료만을 받은 폐암 환자들에 비하여 수술 후 생존 기간이 더 길었다. 표적항암치료를 받은 환자군과 세포독성항암치료만을 받은 환자군 각각에서, RECIST 기준에 따라 항암 치료에 반응이 좋았던 군이 반응하지 않았던 군에 비해 수술 후 생존 기간이 더 길었다.
국소재발률과 수술 관련 합병증 발생률의 경우, 각 군 사이의 비교에서 통계적으로 유의한 결과를 보이지 않았다.
전체 환자 중 총 4명의 환자에서 재수술을 진행하였으며, 재수술 진행률은 세포독성항암치료 군보다 표적항암치료 군에서, en bloc 절제를 진행한 환자군보다 소파술 (curettage)을 진행한 환자군에서 각각 더 높게 나타났다.

이번 연구는 표적항암치료 도입 후 골전이암의 수술적 치료에 변화가 있었는지 살펴보는 데에 목적이 있다. 표적항암치료 군이 세포독성항암치료 군에 비하여 더 생존 기간이 길 것이라는 가설을 세웠고, 생존기간의 향상에 따라 국소 재발률과 수술 관련 합병증이 더욱 증가할 수 있을 것이라고 예상하였다.
표적항암치료를 사용하였을 때, 특히 치료에 반응이 좋았던 경우,

환자들의 생존 기간이 늘어났으며, 추가적으로, 생존 기간의 향상을 보였던 환자 세부 분류군에서 국소재발률과 수술 관련 합병증 발생률이 높은 경향을 확인하였다.
그러나 각 세부 분류군 내 환자수가 충분하지 않았던 점에서 통계적인 유의성이 부족하기에, 연구 결과의 해석을 보다 신중하게 진행하여야 할 것으로 생각한다.

표적항암치료는 골전이암에 대한 수술을 진행한 환자들에게 있어서 수술 후 생존기간을 향상시켰다. 이에 표적항암치료를 진행하는 환자에서, 특히 치료에 반응이 좋은 환자들에게 있어서, 수술방법을 선택하는 데에 있어 오랫동안 지속될 수 있는 체내 삽입물의 안정성을 이전보다 더욱 고려할 필요가 있겠다. 이번 연구에서 살펴본 여러 요인들을 추후 연구에서 발전시켜, 골전이암 환자의 예후를 예측하는 통계적인 모델을 고안에 볼 수 있을 것이다.

주요어 : 표적항암치료, 폐암, 골 전이, RECIST 분류
학 번 : 2020-25910