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Treatment results of intensive care patients with cancer undergoing radiotherapy

Yoğun bakım yatışı sırasında radyoterapi endikasyonu konulan hastalarda tedavi sonuçlarımız

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ABSTRACT

Aim: This paper aims to evaluate the treatment completion status and survival outcomes of patients who were prescribed radiotherapy during intensive care unit (ICU) hospitalization in the radiation oncology clinic.

Material and Method: Data on patients who underwent RT between January 1, 2020, and June 30, 2022, in the Radiation Oncology Clinic of Ankara City Hospital were retrospectively evaluated. The primary endpoint of this study is the patient status at the completion of the planned radiotherapy and the secondary endpoint is the overall survival (OS). The data were recorded and analyzed using SPSS version 26 (IBM Corporation, Armonk, NY, USA).

Results: The data of 11 patients who were indicated for radiotherapy while hospitalized for intensive care between May 20, 2020, and June 30, 2022, in the Ankara City Hospital Radiation Oncology Clinic were retrospectively analyzed. The median follow-up period from the onset of RT was 4.1 months (range 1–9.8). During this period, nine (81.8%) patients had deceased, and two (18.2%) patients were surviving. The median age of the patients was 55 years (range 3–70); four (36.4%) were female and seven (63.6%) were male. Seven (63.6%) of the patients completed the planned radiotherapy scheme and four (36.4%) did not complete the treatment. There was no significant relationship between the inability to complete the treatment and gender (p=0.194) or primary diagnosis (p=0.545). The median OS value of the patients was 4.1 months (range 1–9.8). In addition, the 1-month survival was 60.6%, and the 6-month survival was 20%. There was no significant relationship between OS and age (p=0.401; correlation coefficient: -282) or primary diagnosis (p=0.638). The median OS in women was 5.3 (range 2.7–9.8) months; the median OS in men was 1 month (range 1–5.5; p=0.059). The median OS of those who completed treatment was 4.5 months (range 1–9.8), while that of those who did not complete the treatment was 1.1 months (range 1–4; p=0.037).

Conclusion: Approximately 60% of the patients who were hospitalized in the ICU and indicated for RT were able to complete treatment. A significantly higher OS was achieved in patients who completed the RT protocol. Criteria must be developed when determining the indications for radiotherapy of cancer patients hospitalized in intensive care.

Keywords: Radiotherapy, intensive care unit, palliative

ÖZ

Amaç: Radyasyon onkolojisi kliniğinde yoğun bakım ünitesi (YBÜ) yatışı sırasında radyoterapi endikasyonu konulan hastaların tedavi tamamlama durumunu ve sağkalım sonuçlarını değerlendirmek amaçlanmıştır.

Gereç ve Yöntem: Ankara Şehir Hastanesi Radyasyon Onkolojisi Kliniği'nde 01.01.2020-30.06.2022 tarihleri arasında RT uygulanmış hastaların verileri retrospektif olarak değerlendirilmiştir. Bu araştırmanın primer sonlanım noktası hastaların tedaviyi tamamlama durumudur ve sekonder sonlanım noktası genel sağkalımdır (GS). Veriler SPSS ver. 26 (İBM Corporation, Armonk, NY, USA) kullanılarak kaydedilmiştir ve analiz edilmiştir.

Bulgular: Araştırmamızda Ankara Şehir Hastanesi Radyasyon Onkolojisi Kliniğinde 20.05.2020 - 30.06.2022 tarihleri arasında radyoterapi alan hastalardan, endikasyonu yoğun bakım yatışı sırasında konulmuş olan 11 hastanın verileri retrospektif incelenmiştir. RT başlangıcından itibaren medyan takip süresi 4.1 (range 1-9.8) aydır. Bu süre içinde 9 (81.8%) hasta ex, 2 (18.2%) hasta hayattadır. Hastaların median yaşı 55 (range 3-70); 4 (36.4%) kadın 7 (63.6%)'sı erkektir. Hastaların 7 (%63.6)' si planlanan radyoterapi şemasını tamamlanmıştır ve 4 (36.4%)'ü ise tedaviyi tamamlayamamıştır. Tedaviyi tamamlayamama ile primer tanı (p=0.545) arasında anlamlı ilişki tespit edilememiştir. Hastaların median GS değeri 4.1 (range 1-9.8) aydır Ayrıca 1 aylık sağkalım 60.6 % ve 6 aylık sağkalım 20%'dır. GS ile yaş (p=0.401; correlation coefficient -282) ve primer tanı (p=0.638) arasında anlamlı ilişki yoktur. Kadınlarda median GS 5.3 (range 2.7-9.8) aydır; erkeklerde median GS 1 (range 1-5.5) aydır (p=0.059). Tedaviyi tamamlayanların median GS değeri 4.5 (aralık 1-9.8) ay iken; tedaviyi tamamlayamayanlar median GS 1.1 (range 1-4) aydır (p=0.037).

Sonuç: YBÜ yatışı olup RT endikasyonu konulan hastaların yaklaşık %60'ı tedaviyi tamamlayabilmiştir. Planlanan RT şemasını tamamlayan hastalarda anlamlı olarak daha yüksek GS elde edilmiştir. Yoğun bakım yatışı olan kanser hastalarının radyoterapi endikasyonlarını belirlerken uygulanacak kriterlerin geliştirilmesi gerekmektedir.

Anahtar Kelimeler: Radyoterapi, yoğun bakım ünitesi, palyatif

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INTRODUCTION

Recent advances in cancer treatment have increased survival rates, while new complications may occur due to new treatment modalities (1,2). With the extension of treatment processes and the introduction of new treatment agents, changes in the need for an intensive care unit (ICU) are also being monitored. It has been reported that ICU hospitalizations are gradually increasing due to the treatment-related toxicity of locally advanced cancer cases (3). These hospitalizations may be due to the underlying primary cancer, comorbid diseases, or treatment toxicity. ICU hospitalization is most common in cases of leukemia-lymphoma cancer diagnoses; among solid tumors, it is most common with lung cancer (4).In the ICU, patients are evaluated not only oncologically but also psychosocially (5,6).

Radiation therapy (RT) is one of the cornerstones of the treatment of cancer patients (7,8). It is used in different stages of cancer treatment as primary, adjuvant, and palliative therapy. To perform RT, the patient must be moved to the radiotherapy unit and immobilized in the treatment room. Alongside the increasing need for ICU care among cancer patients and the growing population of patients needing ICU hospitalization, uncertainties in the RT indications of patients in the ICU have become more important than before. Clinicians' general opinion is that patients in the ICU cannot be mobilized to the RT device, which is necessary to apply RT, and immobilization during RT cannot be achieved. So, ICU patients are not indicated for RT until the clinical necessity or the individual condition of the patient has been assessed. Issues such as the expected benefits and toxicity of treatment and the cost of treatment also factor into whether to indicate RT for patients admitted to the ICU. Each patient must be individually assessed for the risks and benefits that will be achieved with treatment. This is especially true for critical patients who will require daily transportation to the RT room from the treatment environment where important interventions can be applied, such as the intensive care unit. Voight et al. (9) reported that in-hospital transportation of cancer patients with ICU hospitalization leads to an increase in hospital and ICU hospitalization time, vasopressin use, and mortality.

Studies on the treatment and follow-up of cancer patients with indications for intensive care are increasingly being conducted (10,11,12). These studies primarily seek to determine the balance between choosing a treatment that will benefit the patient and providing end-of-life care. Different types of cancer, different treatment modalities, different ICU hospitalization indications, and differences in health system policies make it difficult to reach a consensus among studies. Radiotherapy's utility in this group of patients was investigated, in particular, to treat respiratory failure due to malignant obstruction.

RT is a high-cost oncological treatment (13,14). Developments in the field of radiotherapy and case studies including metastatic disease give hope (15,16,17). To evaluate the effect of RT in patients who have been admitted to the ICU, it is important to consider both the necessity of mobilizing patients from the ICU and the regulation of oncological treatment costs. If RT contributes to the health of this group of patients, they should not be deprived of effective treatment only because of ICU hospitalization; if it is ineffective, high-cost treatment should not be forced, although it may reduce patients' comfort. This research topic, which is not yet well represented in the literature, will be examined retrospectively with data from a single center. This study aims to report the characteristics of patients who were prescribed radiotherapy during ICU hospitalization in the radiation oncology clinic, their treatment completion status, and treatment and survival results.

MATERIAL AND METHOD

Data from patients who underwent RT between January 1, 2020, and June 30, 2022, in the Radiation Oncology Clinic of Ankara City Hospital were retrospectively evaluated. The study was initiated with the approval by the Ankara City Hospital Hospital Clinical Research Ethics Committee (Date: 27.07.2022, Decision No: 2787). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patient interview information, patient files, and electronic system data were used for the study. Patient age, gender, primary disease, pathological data, disease stage and treatment details, performance status, presence of comorbid disease, other simultaneous medical treatments administered during RT, RT dose and fraction details, RT completion status, RT-related acute side effects, and final patient status were noted.

Patient Selection

Patients who were directed to our clinic during hospitalization in the Ankara City Hospital ICU, diagnosed with cancer with pathological evidence and indicated for RT, and whose file data were complete were included in the study. The main goal of the research is the indication of RT in patients with ICU hospitalization. Therefore, patients with ICU hospitalization were examined at the stage when the RT decision was made. Patients who were not in intensive care at the beginning of RT and were admitted to the ICU during treatment or who had missing file data were excluded.

Primary and Secondary Endpoints of the Study

The primary endpoint of the study is the status of patients' completion of the planned radiotherapy schedule. The secondary endpoint of the study is general survival (OS).

The RT end date was considered the start date for the OS. The endpoint for the OS is the last control date for living patients and the exitus date for deceased patients.

Statistical Analysis

The data were recorded and analyzed using SPSS version 26 (IBM Corporation, Armonk, NY, USA). The categorical demographic characteristics of the patients were calculated with chi-squared and Fisher's exact tests. Kolmogorov–Smirnov and Shapiro–Wilk tests were used to check the suitability of the data for normal distribution. Nonparametric tests were used because the data did not seem to fit the normal distribution.

Spearman's correlation test was used to evaluate the correlation between the numerical variables. Kaplan–Meier was used in the univariate survey analyses and comparisons were made with the log-rank test. In the multivariate analyses, a Cox regression test was used and the significance limit was accepted as ≤ 0.05.

RESULTS

In our study, the data of 11 patients whose radiotherapy indication was placed during intensive care hospitalization between May 20, 2020, and June 30, 2022, at Ankara City Hospital Radiation Oncology Clinic were retrospectively analyzed. The causes of patients' ICU hospitalization include intracranial hematoma, pulmonary thromboembolism, vaginal bleeding, sepsis, status epilepticus, hypoxia, and general condition disorders.

The median follow-up period from the onset of RT was 4.1 months (range 1–9.8). During this period, nine (81.8%) patients had deceased and two (18.2%) were alive. The median age of the patients was 55 years (range 3–70); four (36.4%) were female and seven (63.6%) were male. Five (45.5%) of the patients received palliative RT due to brain metastasis. The patients' demographic data, disease details, and treatment details are summarized in **Table 1** and **Table 2**.

Seven (63.6%) of the patients completed the treatment and four (36.4%) did not. The reasons for the inability to continue treatment were the need for mechanical ventilation. There was no significant relationship between the inability to complete treatment and the primary diagnosis (p=0.545). The median OS value of the patients during the follow-up period was 4.1 months (range 1–9.8) (**Figure 1**). In addition, the 1-month survival is 60.6%; the 2-month survival is 50.5%; the 3-month survival is 40.4%, and the 6-month survival is 20%.

Table 1. Patient and treatment details

Parameters		
Age	55 (3-70)	
Gender		
Female	4	(36.4%)
Male	7	(63.6%)
Primary		
BM	5	(45.5%)
Others	6	(54.5%)
RT indication		
BM	6	(54.5%)
Vaginal bleeding	2	(18.2%)
Hypoxia	2	(18.2%)
Adjuvant	1	(9.1%)
ICU indication		
Intracranial hemorrhage	3	(27.3%)
Pulmonary thromboembolism	2	(18.2%)
Hypoxia	2	(18.2%)
Vaginal bleeding	1	(9.1%)
Status epilepticus	1	(9.1%)
Sepsis	1	(9.1%)
Postoperative	1	(9.1%)
Completion of treatment		
Treatment completed	7	(63.6%)
Treatment not completed	4	(36.4%)
Last status		
Exitus	9	(81.8%)
Alive	2	(18.2%)

Abbreviations: BM=Brain Metastasis

Table 2. Patients and treatment characteristics

Patient	Diagnose	Palliative treatment intent	Prescribed dose	Given fraction number	Last status
Male, 3 yo	Neuroblastoma	Brain metastasis	150 cGyx10 frc	3	Ex
Female, 55 yo	Renal cell cancer, lung metastasis	Hemoptysis	500cGyx4 frc	4	Ex
Male, 10 yo	High grade B cell lymphoma, brain involvement	Brain involvement	180 cGY x 13 frc	1	Ex
Male, 70 yo	Unknown primary with brain metastasis	Brain metastasis	400 cGY x 5 frc	0	Ex
Male, 63 yo	Metastatic lung cancer	Shortness of breath	400 cGy x 5 frc	5	Ex
Female, 49 yo	Metastatic thyroid cancer	Shortness of breath	300cGy x 18 frc	18	Alive
Male, 66 yo	Endometrial cancer with lung metastasis	Vaginal bleeding	400 cGyx 5 frc	5	Ex
Female, 47 yo	Lung cancer with brain metastasis	Brain metastasis	800cGy x 1 frc	1	Ex
Male, 56 yo	Glioblastom	Inoperable mass	300 cGy x 10 frc	2	Ex
Female, 57 yo	Recurrent endometrial cancer	Vaginal bleeding	500 cGy x 5 frc	5	Ex
Male, 52 yo	Lung cancer with bone and brain metastasis	Brain metastasis	400 cGy x 5 frc	5	Alive

Abbreviations: yo: years old; cGy: santigray; frc: fractions; ex:exitus

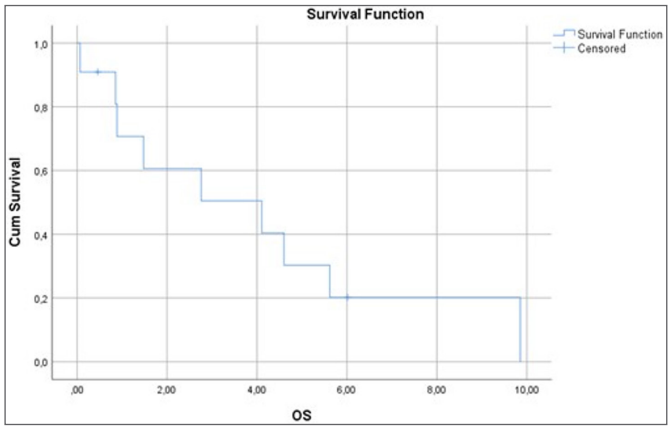

Figure 1. Results of Kaplan-Meier analysis of overall survival of patients

When OS-influencing factors were evaluated, there was no significant correlation between the age of the patients and OS (p=0.401; correlation coefficient: -282). There was also no statistically significant relationship between the patients' primary diagnoses and OS (p=0.638). When compared by gender; the median OS in females was 5.3 months (range 2.7–9.8), and the median OS in males was 1 month (range 1–5.5; p=0.059). A median OS of approximately 4.5 months more was obtained in women than in men, and the difference is close to the significance limit (**Figure 2,3**). With an increased number of patients, this difference may become significant.

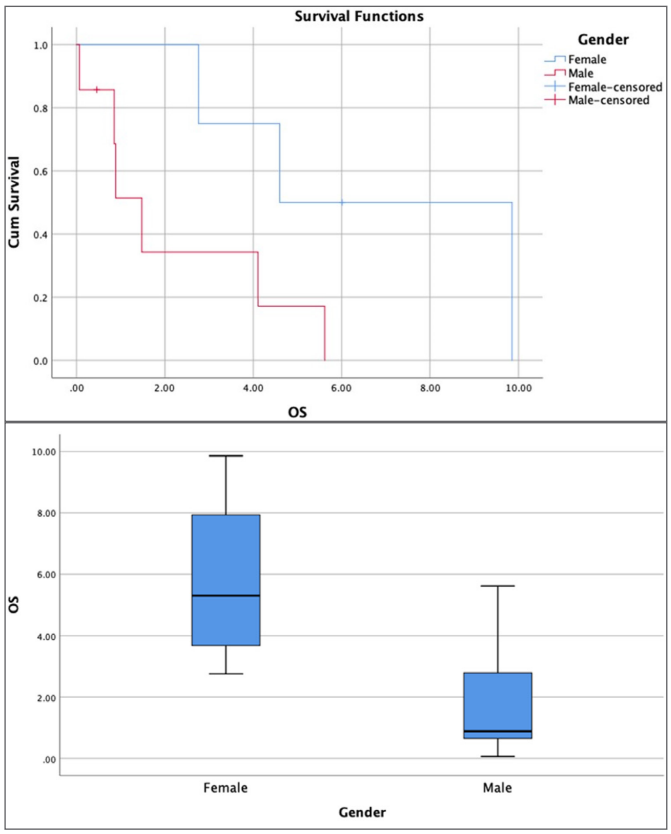

Figure 2,3. The Relationship between gender and OS

When those who completed the treatment and those who could not complete it were examined; the median OS of those who completed the treatment was 4.5 months (range 1–9.8); those who did not complete treatment had a median OS of 1.1 months (range 1–4). Those who completed the treatment lived significantly longer. All of the patients who could not complete the treatment had deceased within 1–4 months; the remaining two patients were in the group that completed treatment (p=0.037) (**Figure 4,5**).

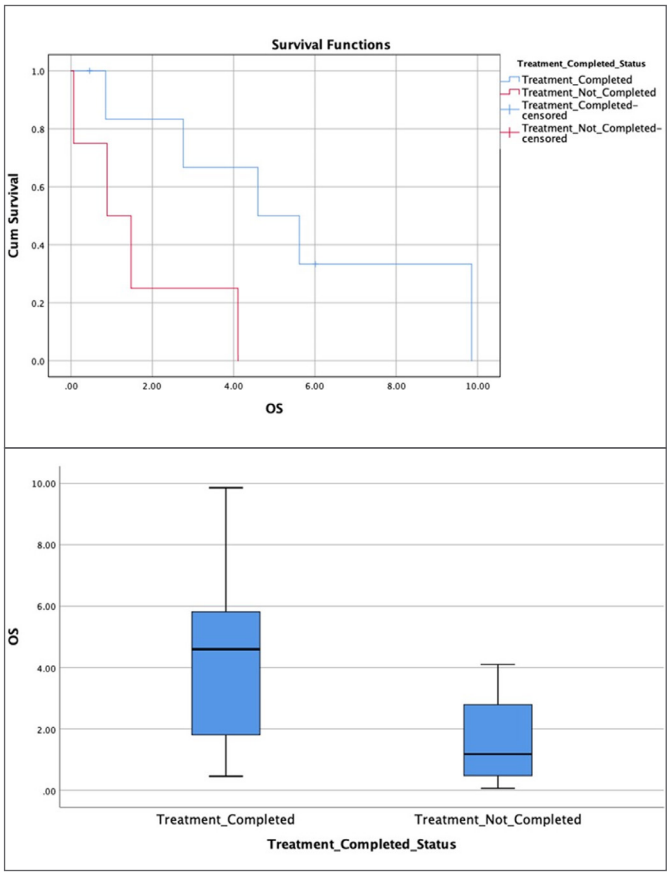

Figure 4,5. The Relationship between status of treatment completion and OS

DISCUSSION

This study aimed to examine the completion of the planned treatment and the overall survival rates of cancer patients who were indicated for radiotherapy during ICU hospitalization. According to the study findings, 63.6% of the patients were able to complete the treatment. The median survival of patients was 4 months, and the 6-month survival was 20%. The median OS in women is 4 months greater than in men (5.8 months vs. 1 month), and this difference is close to the significance limit. A significantly higher OS was obtained in those patients who completed treatment (p=0.037).

With the new developments in cancer treatment, changes in the ICU admission patterns of these patients have been observed over time.

The main important factors in this change are increased survival times and the new toxic complications that develop with new treatments. In Vigneron et al.'s study, the ICU admission of cases with solid malignancies was reported (3). The ICU admission status of 1,525 patients with solid tumor diagnoses was evaluated in a single-center study, and the lungs and gastrointestinal system were reported as the most common primary tumor sites. Another important point reported is a recent increase in the ICU admissions of metastatic patients, and this increase is generally due to drug and treatment-related toxicity. In this study, the 1-year OS rate was 33.2% in patients whose follow-up was completed.

Although there is an increase in ICU admissions of cancer cases, the mortality of these patients is reportedly two times higher than that of non-cancer patients (18). Recent studies and guidelines have advanced toward correctly evaluating which cancer patients are suitable for ICU admission (19). Two main elements are involved in the decision to admit patients to the ICU and apply the treatment: The first is whether the treatment that is planned for a cancer patient in the intensive care unit will prolong life at an acceptable level or contribute to the patient's symptom palliation, and the second is whether the planned treatment and ICU hospitalization will make the time until death more distressing. The balance between these two factors should be calculated carefully when deciding on the hospitalization and treatment of the patient.

As mentioned above, current studies are moving toward determining which patients will benefit from ICU admission. In a review published by the European Society for Medical Oncology, patients who are recommended for admittance to the ICU are cases in remission, newly diagnosed cancer cases with a life expectancy of more than 1 year, patients requiring ICU admission due to OCT complications, and cases of locally advanced solid tumors with a life expectancy of more than 1 year (19). The development of these and similar criteria for patients who will be treated during ICU hospitalization may prevent unnecessary treatment applications.

Another factor that may be important in establishing a cancer treatment indication among ICU admissions is the chosen treatment modality and purpose of treatment. Radiotherapy is an important component of palliative therapy (20,21). The literature on radiotherapy indication that is relevant to this article generally includes studies evaluating palliative irradiation due to malignant airway obstruction (16,17).

Louie et al. (16), who have published important studies on this subject, report that 26 patients who were offered palliative RT due to malignant obstruction were retrospectively examined. In terms of overall survival and extubation success, the median survival was reported as 0.36 months (range 0–113 months). The 6-month overall survival (OS) was reported as 11%. In our study, which uses a very different patient population and sample size, the reported 6-month OS was 20%. Researchers have reported a relationship between an increase in the applied radiation dose and survival. In Assi et al.'s study, in which the ICU hospitalizations of cancer cases were evaluated in general, the median OS reported was 22 days (12). This suggests that palliative radiotherapy applications may be beneficial in this patient group. In addition, evaluating the subject in terms of patient palliation and the achievement of the palliation target are elements that will be useful in making the treatment decision. Due to the retrospective nature of the study, this evaluation could not be made or reported for these patients.

This study has many limitations in terms of adequate evaluation of the subject. First, this is a retrospective and single-center study with a small number of cases. In our clinic, which is a new center, a common criterion has not yet been determined for these patients and the determination of treatment indications is clinician-dependent. The heterogeneity of the patient group in terms of diagnosis, age, and purpose of RT makes it difficult to reach a consensus. In addition to these limitations, the positive effect of the completion of the planned treatment on survival emphasizes the importance of evaluating patients from this perspective.

CONCLUSION

Despite its shortcomings, this cohort data, which comprised mainly brain metastasis cases, was expected to contribute usefully due to the limited literature data on the subject. Prospective and planned studies with homogeneous patient groups are needed on this subject.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Health Sciences University Ankara City Hospital No: 1 Clinical Researches Ethics Committee (Date: 27.07.2022, Decision No: E1-22-2787).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

REFERENCES

1. Martins F, Sofiya L, Sykiotis GP, et al. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. Nat Rev Clin Oncol 2019; 16: 563–80.
2. Debela DT, Muzazu SG, Heraro KD, et al. New approaches and procedures for cancer treatment: Current perspectives. SAGE Open Med 2021; 9: 20503121211034366.
3. Vigneron C, Charpentier J, Valade S, et al. Patterns of ICU admissions and outcomes in patients with solid malignancies over the revolution of cancer treatment. Ann Intensive Care 2021; 11: 182.
4. Kress JP, Christenson J, Pohlman AS, et al. Outcomes of critically ill cancer patients in a university hospital setting. Am J Respir Crit Care Med 1999; 160: 1957-61.
5. Yıldız M, Çelik D, Çakır M, Savaşır T. Yoğun bakım ünitesi ve palyatif bakım servisinde çalışan hekim ve hemşirelerinin iyi ölüme ve saygın ölüm ilkelerine ilişkin tutumları . Journal of Medicine and Palliative Care 2021; 2: 77-85 .
6. Aslan Y. Palyatif bakımda psikososyal yaklaşım ve değerlendirme. J Med Palliat Care 2020; 1: 41-5.
7. Baskar R, Lee KA, Yeo R, et al. Cancer and radiation therapy: current advances and future directions. Int J Med Sci 2012; 9: 193-9.
8. Sampath S. Treatment: Radiation Therapy. Cancer Treat Res 2016; 170: 105-18.
9. Voigt LP, Pastores SM, Raoof ND, et al. Review of a large clinical series: intrahospital transport of critically ill patients: outcomes,timing, and patterns. J Intensive Care Med 2009; 24: 108–15.
10. Hong Y, Hong JY, Park J. Differences in ICU outcomes according to the type of anticancer drug in lung cancer patients. Front Med (Lausanne) 2022; 9: 824266.
11. Lecuyer L, Chevret S, Thierry G, et al. The ICU trial: a new admission policy for cancer patients requiring mechanical ventilation. Crit Care Med 2007; 35: 808-14.
12. Assi HI, Halim NA, Alameh I, et al. Outcomes of patients with malignancy admitted to the intensive care units: a prospective study. Crit Care Res Pract 2021; 2021: 4792309.
13. Mittmann N, Liu N, Cheng SY,et al. Health system costs for cancer medications and radiation treatment in Ontario for the 4 most common cancers: a retrospective cohort study. CMAJ Open 2020; 8: 191-8.
14. Van Dyk J, Zubizarreta E, Lievens Y. Cost evaluation to optimise radiation therapy implementation in different income settings: A time-driven activity-based analysis. Radiother Oncol 2017; 125: 178-85.
15. Rodrigues G, Videtic GM, Sur R, et al. Palliative thoracic radiotherapy in lung cancer: An American Society for Radiation oncology evidence-based clinical practice guideline. Pract Radiat Oncol 2011; 1: 60-71.
16. Louie AV, Lane S, Palma DA, Warner A, Cao JQ, Rodrigues GB. Radiotherapy for intubated patients with malignant airway obstruction: futile or facilitating extubation? J Thorac Oncol 2013; 8: 1365-70.
17. Louie AV, Li L, Jenkyn KB, et al. A population-based analysis of outcomes after radiotherapy in intensive care unit patients with lung cancer. J Thorac Dis 2018; 10: 1440-8.
18. Taccone FS, Artigas AA, Sprung CL, Moreno R, Sakr Y, Vincent JL. Characteristics and outcomes of cancer patients in European ICUs. Crit Care 2009; 13: 15.
19. Schellongowski P, Sperr WR, Wohlfarth P, et al. Critically ill patients with cancer: chances and limitations of intensive care medicine-a narrative review. ESMO Open 2016; 1: e000018.
20. Spencer K, Parrish R, Barton R, et al. Palliative radiotherapy. BMJ 2018; 360: 821.
21. Arscott WT, Emmett J, Ghiam AF, et al. Palliative radiotherapy: inpatients, outpatients, and the changing role of supportive care in radiation oncology. Hematol Oncol Clin North Am 2020; 34: 253-77.