Literature Review

Role of radiotherapy in oncologic emergency

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ABSTRACT

Background: Oncologic emergencies often occur in patients who have metastases. This condition requires a prompt and accurate diagnosis. Radiotherapy (RT) plays a substantial role in palliative aspect with the aim of reducing tumor size, reducing symptoms, and improving quality of life. **Purpose:** To discuss the role of RT in an oncologic emergency, by focusing on superior vena cava syndrome, uncontrolled tumor bleeding, spinal cord compression due to malignancy, and brain metastases. **Literature review:** Through PubMed, Medscape, ResearchGate, and Springer databases, this systematic review was searched from 2015-2022 using keywords: "radiologic therapy", AND "oncologic emergencies", AND "superior vena cava syndrome", AND "uncontrolled tumor bleeding", AND "spinal cord compression", AND "brain metastases". **Result:** The authors made a meta-analysis using all the keywords, and from 34 screened researches, only 30 articles were included in the reference. **Conclusion:** Radiotherapy plays a significant role in oncologic emergency, particularly to reduce symptoms and improve quality of life. Several considerations should be evaluated before determining the appropriate radiation treatment such as patient factors, previous radiation therapy, and response to prior systemic therapy.

Keywords: emergency, oncology, radiotherapy

ABSTRAK

Latar belakang: *Kegawatdaruratan onkologi paling sering terjadi pada pasien yang memiliki metastasis. Kondisi ini memerlukan diagnosis yang cepat dan akurat. Radioterapi mempunyai peran penting dalam aspek paliatif dengan tujuan mengecilkan ukuran tumor, mengurangi gejala, dan meningkatkan kualitas hidup.* ***Tujuan:*** *Membahas peran radioterapi dalam kegawatdaruratan onkologi.* ***Tinjauan pustaka:****Dilakukan meta-analisis melalui beberapa basis data seperti:* PubMed, Cochrane, Embase, and Proquest; *menggunakan kata kunci:* "radiologic therapy", *DAN* "oncologic emergencies", *DAN* "superior vena cava syndrome", *DAN* "uncontrolled tumor bleeding", *DAN* "spinal cord compression", *DAN* "brain metastases". ***Hasil:*** *Berdasarkan pencarian literatur diperoleh 744 artikel, yang didapat dari* Pubmed *607 artikel, dari* Cochrane *2 artikel, dari* Embase *103 artikel, dan dari* Proquest *32 artikel. Berdasarkan skrining judul, didapati 35 artikel yang sesuai dengan topik tinjauan pustaka ini. Melalui meta-analisis, 30 artikel dapat dimasukkan ke dalam tinjauan pustaka.Kasus gawatdarurat yang membutuhkan radioterapi antara lain sindroma vena cava superior, perdarahan tumor tidak terkontrol, kompresi sumsum tulang belakang akibat keganasan, dan metastasis ke otak. Dalam pemilihan dosis dan teknik radioterapi yang akan diterapkan, harus disesuaikan dengan kondisi pasien.* ***Kesimpulan:*** *Radioterapi berperan penting dalam kegawatdaruratan onkologi, khususnya untuk mengurangi keluhan dan meningkatkan kualitas hidup. Perlu dipertimbangkan faktor pasien, riwayat radias**i** dan respon terhadap pengobatan sistemik sebelumnya dalam menentukan tatalaksana radiasi yang tepat.*

Kata kunci: *kegawatdaruratan, onkologi, radioterapi*

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INTRODUCTION

Oncologic emergency is a potentially life threatening acute condition, both directly and indirectly in relation with the cancer or the treatment.[1] This medical condition may threaten organ function in a reversible manner which require treatment within hours following diagnosis.[2] Once an oncologic emergency is identified, the appropriate treatment depend on the reversibility of the condition, life expectancy and survival, and the most effective palliative modality.[1]

In general, with the advancement of cancer treatment, patient survival has been improving, and therefore the incidence of oncologic emergencies is increasing.[3] On the other hand, several oncologic emergency cases were not correctly and promptly diagnosed leading to severe clinical manifestations. These clinical manifestations may develop in a few hours heading to outcomes of disability to death.[4] Not much different from other medical emergencies, oncologic emergencies also require prompt and accurate diagnosis and multidisciplinary treatment. The role of radiotherapy in the treatment of oncologic emergencies is crucial to provide effective care and limiting morbidity and disease progression.[5] However, to date, publications regarding the role of radiotherapy are still limited, and the standard of care is yet to be defined. This article focused on the most common oncologic emergencies including spinal cord compression, superior vena cava obstruction, brain metastasis, and tumor bleeding; and the role of radiation oncology in the management of the respective disease entities.

LITERATURE REVIEW

Method

The searching process was conducted throughout several journal databases such as PubMed, Cochrane, Embase, and Proquest; using keywords: “radiologic therapy”, AND “oncologic emergencies”, AND “superior vena cava syndrome”, AND “uncontrolled tumor bleeding”, AND “spinal cord compression”, AND “brain metastases”. Both primary and secondary studies comprising various range of metabolic, hematologic, structural, and medication-induced oncologic manfestations were included. The exclusion criteria were studies among pediatric population, and studies which elaborated the combination of chemo-radiotherapy regiments.

Result

Based on the literature search, there were sum up to 744 journal articles, consisted of 607 PubMed articles, 2 Cochrane articles, 103 Embase articles, and 32 Proquest articles. Based on the title screening, it was found a total of 35 articles which seemingly fit to this study topic. After meta-analysis, 30 articles were included for this review.

Types of oncologic emergency

In general, oncologic emergencies can result from metabolic, hematologic, structural, and treatment-related disorders.[1] Several types of oncologic emergencies are listed in Table 1.

Table 1. Summary of oncologic emergencies

Types of oncologic emergency	Associated cancer or cause of oncologic emergency
Metabolic	
Tumor lysis syndrome	Hematologic malignancies including acute leukemia and lymphoma, and solid tumors
Hypercalcemia in malignancy	Multiple myeloma, breast cancer, head-and-neck, cervical and lung squamous cell carcinoma
Hematologic	
Febrile neutropenia	Chemotherapy
Hyperviscosity syndrome	Leukemia, multiple myeloma
Acute bleeding	Thrombocytopenia, vascular infiltration of tumors, disseminated intravascular coagulation, localized infection at tumor site
Structural	
Superior vena cava syndrome	Mediastinal malignancy, lymphoma, metastatic tumor, benign mediastinal tumor, vascular disorder, infection, thrombosis, mediastinal fibrosis
Spinal cord compression	Primary tumor of breast cancer, lung cancer, prostate cancer, and cancers of unknown primary origin
Increased intracranial pressure	Primary and metastatic brain tumors
Treatment side effects	
Diarrhea	Chemotherapy
Extravasation	Intravenous (IV) chemotherapy
Obstipation	Opioid medication, chemotherapy

Table 2. Classification for spinal instability neoplastic score.[22]

Component	Score
Location	
Junctional (O-C2;C7-T2;T11-L1;L5-S1)	3
Mobile spine (C3-6; L2-4)	2
Semirigid (T3-10)	1
Rigid (S2-S5)	0
Mechanical pain	
Yes	3
No	2
Pain free lesion	1
Bone lesion	
Lytic	2
Mixed (lytic/blastic)	1
Blastic	0
Radiographic spinal alignment	
Subluxation/translation present	4
Deformity (kyphosis/scoliosis)	2
Normal	0
Vertebral body collapse	
>50% collapse	3
<50% collapse	2

No collapse with >50% body involved	1
None of the above	0
Postero-lateral involvement	
Bilateral	3
Unilateral	1
None of the above	0

Total score of 1-6 : stable
Total score of 7-12 : possibly impending instability (considered for surgical intervention)
Total score of 13-18 : unstable (surgical intervention is recommended)

DISCUSSION

This article focused on the most common oncologic emergencies including superior vena cava obstruction, tumor bleeding, spinal cord compression, and brain metastasis; and also the role of radiation oncology in the management of the respective disease entities.

Superior Vena Cava Syndrome (SVCS)

SVCS is a condition in which the superior vena cava is obstructed due to extrinsic or intrinsic cause (i.e. tumor compression or thrombus). The most common etiology is malignancy (60% of the cases). The malignancy with the highest incidence are non-small cell lung cancer (NSCLC) which was 50% of cases, followed by small cell lung cancer (SCLC) which was 22%, lymphoma 12%, metastases 9%, germinal cell tumor 3%, and thymoma 2%.[6] Aside from malignancies, SVCS can also be caused by other medical conditions such as iatrogenic thrombosis, or stenosis due to the wire of cardiac pace maker of intravascular catheter for hemodialysis access, antibiotics, or chemotherapy. Diagnosis of SVCS can be made by identification of the clinical signs and symptoms which include facial edema, upper limb edema, distended neck veins, thoracic wall venectation, dyspnea, cough, hoarseness, flushed face (facial plethora), syncope, headache, dizziness, stridor, disorientation, and visual impairment. Out of those signs and symptoms, three of the most common were facial edema (82%), followed by upper limb edema, and distended neck vein (46% and 63%, respectively).[7,8]

Patients suspected with SVCS should undergo radiologic examination. Plain chest X-ray is the most common examination and in 84% of the cases, a mediastinal enlargement was found. Moreover, a more specific imaging technique using thoracic CT scan can be done to determine the severity of obstruction of superior vena cava, the etiology of obstruction, the surrounding structures of the vein, and the collateral vascularization that developed. CT scan had a specificity of 92% and sensitivity of 96% in diagnosing SVCS. Venography is the gold standard for visualizing and diagnosing venous obstruction. This modality can be used simultaneously with intravascular ring placement procedure.[9]

As SVCS is diagnosed, the treatment is chosen based on the symptoms, cancer stage, the patient's general condition, and comorbidities.[7] Initial supportive treatment which can be applied following clinical diagnosis are head elevation on a bed, ABCs (Airway, Breathing, Circulation) control, and diuretics in case of brain edema. Steroids can also be administered particularly in patients with compromised airways, or as a prophylaxis for radiation-induced edema.[10] In life threatening SVCS cases such as severe laryngeal edema or altered mental status/coma due to brain edema, immediate intervention is indicated before proceeding to further step

to determine the cause which was pathologic examination. Intervention of intravascular ring placement is a safe procedure which provides rapid clinical response. Radiation plays a role when ring placement is not feasible in life threatening cases.[7]

To date, the optimal radiation dose in SVCS has yet to be defined. It had been implemented high fractional doses of 3-4 Gy in 3 fractions and conventional fractional dose of 5 Gy in 5 fractions, which produced similar response of improvement of symptoms in 2 weeks. There were also other doses including 4 Gy in 5 fractions.[11,12] The consideration of administration and fractionation can be adjusted with clinical judgement of the radiation oncology specialist. Treatment response of patients with SVCS usually ranges between 7-15 days, however, a more rapid response can be observed in 72 hours following the first radiation. It depends on the histologic characteristics of the tumor causing SVCS. Although the symptoms will improve following radiation, the radiation given in SVCS will not normalize the vascular flow. Patients with SVCS due to malignancy are known to have an average survival of 6 months, nevertheless the prognosis is largely dependent on the etiology rather than the symptoms of SVCS experienced by the patient.[10]

Uncontrolled tumor bleeding

Uncontrolled tumor bleeding is a life-threatening condition with clinical manifestations of epistaxis, hemoptysis, hematemesis, hematochezia, melena, hematuria, vaginal bleeding, and skin lesions. In general, the location of tumor bleeding mostly occurs in large sized tumors with large necrotic area. This condition leads to local bleeding. The bleeding is caused by local invasion of tumors or abnormal vascularization of tumor which potentially lead to uncontrolled bleeding. Tumors with this bleeding characteristics often occur in breast cancer with large tumor mass on the chest wall, localized advanced cervical cancer, and bleeding of intra-abdominal tumor such as sarcoma and gynecologic tumors.[13] However, haemorrhage is also could be found in head and neck cancer, and can occur as major bleeding or on-going low volume oozing.[14]

In the case of tumor bleeding, it is crucial to evaluate the underlying cause. A comprehensive history must be taken to identify the factors that could cause the bleeding. History of consumption of non-steroidal anti-inflammatory drugs, prophylactic anticoagulant therapy, and other chronic comorbidities are important to note. Moreover, laboratory work up for complete blood count and coagulation tests should be done to determine whether or not the bleeding was caused by a systemic disorder. Supporting examinations including angiography, endoscopy, CT scan or MRI can also be done as indicated to determine the specific location of the tumor.[15]

In the treatment of bleeding of tumors, the general principle is to determine the source of bleeding, whether it is an external or internal bleeding, then assess the vital signs. In cases of hypotensive patient, fluid resuscitation should be started while proceeding with work up. In cases in which bleeding caused by coagulation factors, systemic intervention can be taken. In cases of external bleeding, hemostatic wound dressing can be applied on the source of bleeding and then re-evaluate whether the bleeding is still active or not. If the bleeding is uncontrolled, then the patient can be referred to radiotherapy for further treatment. In cases with internal source of bleeding, the treatment is generally based on bleeding location and it can be considered for referral to radiotherapy in an unresolved condition.[13,15] Bleeding control following radiotherapy can reach up to 85%.[16]

In regard of radiation dose, there are several choices for radiation dose which can be given to treat bleeding, including hypofractionation of 20 Gy in 5 fractions or 8-10 Gy in 10 fractions, 17 Gy in 2 fractions done 1 week apart for hemoptysis; hypofractionation of 20 Gy in 5 fractions or 7 Gy per fraction which can be repeated every week up to a total dose of 21 Gy for vaginal, gastrointestinal and urinary tract bleeding.[13] Study from Sapienza et al.[16] tried to compare radiotherapy dose in the case of uncontrolled bleeding. In their study, there were 112 cancer patients with bleeding, where 17 of patients were from head and neck malignancies. Radiotherapy dose given ranging from 20 Gy in 5 fractions, 30 Gy in 10 fractions, and 8 Gy in a single fraction. Successful rates of primary bleeding control for head and neck region was 88% (14/16). Based on that study, it was suggested that long fractionation regimens (>5 fractions) were not associated with a reduced incidence of re-bleeding (p=0.65), but were associated with more treatment interruptions (p=0.02). Therefore, short fractionation (<5 fractions) is preferable in bleeding case, with consideration to minimize the treatment burden for patients.[16,17]

Spinal cord compression due to malignancy

Spinal cord compression (SCC) is a condition in which the mass of metastatic tumor or a local tumor expand locally both extradural and intradural which lead to compression of dura sac and its content to the spinal cord. This resulted in irreversible neurological damage including tetraplegia and paraplegia depending on the location and level of lesion.[18] SCC often occurs in 5% of patients within their last 2 years of life expectancy. The most common cause of SCC are bone metastases in breast cancer (29%), lung cancer (17%), and prostate cancer (14%). Due to the possibility of irreversible neurological damage, any pain and progressive neurological disorder in 48 hours should be evaluated for the possibility of SCC.[19,20]

In SCC, pain is the initial symptom of spinal cord compression, thus require further evaluation.[20] The pain can be a localized pain due to local inflammation, radicular pain due to compression on the radix, and mechanical pain which are worsen by movement. Mechanical pain indicate that the pain originated from the bones, from a collapse or compression of vertebral body. Other than pain, neurological disorder such as sensory, motor and autonomic nervous systems disorder are the most common symptoms. The neurological disorder that arises usually indicate a high severity of epidural compression. The onset of pain and progressive neurological disorder in 48 hours should be further evaluated with physical examination including gait, motor, sensory functions and reflexes.[21]

MRI is the gold standard to determine the severity of spinal cord compression. MRI is required to visualize the location of epidural compression and the severity of compression which can be evaluated on the T1-weighted axial and sagittal plane with or without contrast and also on T2-weighted. Other imaging technique which can be done are vertebral CT scan and plain vertebral X-ray. Vertebral CT can be performed to evaluate the compression of the fracture, mechanical instability or protrusion of a bone fragment posteriorly. A plain vertebral X-ray can determine the severity of bone destruction both osteoblastic and osteolytic, vertebral collapse, or subluxation.[13,22]

The treatments required in this medical emergency condition are radiation and surgery.[19] As an initial therapy, steroids can be given once diagnosis is made along with supportive treatments.[21] The decision for surgery can be made using the Spinal Instability Neoplastic Score (SINS Score) classification. Emergency radiotherapy has yet a clear definition, however in a study by

Rief et al.[19], within 12 hours after the onset of acute neurologic deficits, if not treated promptly it will cause permanent sensory-motor disorder. The radiotherapy dose given would be 10x3 Gy, 5x4 Gy, 1x8 Gy, or 15x2.5 Gy.[13]

Evidence of RT in managing SCC of head and neck cancer, despite being scarce, can be found in several studies. Rades et al.[23] showed that 2 out of 9 patients (22.2%) with salivary glands carcinoma have an improved motor function after SCC radiation. Despite a small percentage of improved function, there are several factors that need to be considered in order to predict the post-radiation ambulatory status of patients. In other studies of 60 head-and-neck cancer patients, post-ambulatory status was affected by the length of developing motor deficits (more than 7 days), able to ambulate before RT and ECOG performance score (score of 1-2) with a higher points will result in higher chance of post-RT ambulatory rate.[24] Moreover, when combine with surgery, a meta-analysis showed that RT produced better clinical ambulatory outcome compared with RT alone (relative risk/RR: 1.43; 95% Confidence Interval/CI: 1.14-1.78). Surgery followed by RT also produced a significant 6-month survival rate (RR: 1.21; 95% CI: 1.09-1.33).[25]

Brain metastases

Brain metastases is a condition in which cancer cells of a primary tumor in another organ have spread to the brain. Brain metastases may lead to neurological deficits and seizures. This condition will become an oncologic emergency when there is an increased intracranial pressure and status epilepticus. The most common origin of brain metastases are lung cancer, breast cancer, and melanoma. Altogether, these three types of cancer comprise up to 70-90% of brain metastases case. Another common etiology of brain metastases are renal cell carcinoma and colorectal cancer.[26]

Patients with brain metastases will develop several neurological symptoms including headache, epileptic seizure, hemiparesis, hemisensory loss, behavioral changes, aphasia, visual impairment, and signs of increased intracranial pressure.[27] As for the symptoms of emergent increased intracranial pressure are headache, vomiting, altered mental status from somnolence to coma. In conditions when brain herniation is present, hypertension, bradycardia and irregular respiration (Cushing's triad) can be observed.[27,28]

Other oncologic emergency condition to watch out for is status epilepticus.[29] Supporting investigations that can be performed in patients with brain metastases are CT scan or MRI.[13] In case of oncologic emergency due to increased intracranial pressure, the initial treatment is administration of high-dose corticosteroids. While in oncologic emergency due to status epilepticus, the initial treatment is anticonvulsant therapy. Thereafter, the patient can be consulted to radiotherapy for further treatment. Radiotherapy intervention with Whole Brain Radiotherapy (WBRT) and/or Stereotactic Radiotherapy (SRT), although no effect on overall survival, are able to improve local control of brain metastasis. As for the radiotherapy regiments for WBRT in brain metastases are 20-30 Gy in 5-10 fractions. There was no significant distinction in overall survival, disease-free survival, or brain metastasis-related death among various WBRT fractionation schedules. In addition to WBRT, Stereotactic Radiosurgery can also be considered particularly for patients with multiple metastatic lesions of 1-4 lesions or 5-10 lesions with a cumulative tumor volume of <15 mL.[28,30]

In conclusion, radiotherapy plays a substantial role in oncologic emergencies. The role of radiotherapy mostly as a palliative treatment to reduce symptoms and improve quality of life. In determining emergency indications, the authors took into

consideration the factors associated to the patient's circumstances such as poor general condition, the possibility of receiving curative treatment, severe comorbidities, factors associated with the cancer including the cancer histology, and factors correlated with treatment including history of prior radiation therapy and response to previous systemic therapy.

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