

Review Article

Role of external beam radiotherapy in oncologic emergencies.

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Abstract

There has been increased incidence of oncologic emergencies along with diagnosis of malignancy. Prompt evaluation is crucial to avoid worsening of conditions. Complete oncologic evaluation should be planned by tumor board panel and optimal local and systemic approach is to be considered. Not all patients are able to undergo surgery or invasive procedure due to multiple systemic progression and compromised performance status. External beam radiotherapy is beneficial in various conditions; brain metastasis, spinal metastasis, superior vena cava obstruction, tumor hemorrhage and cancer pain.

Key words: Oncologic emergencies, External beam radiotherapy

Received: 18 June 2018

Revised: 10 April 2019

Accepted: 17 April 2019

Introduction

Oncologic emergency is the clinical presentation of cancer patients that need prompt medical attention. It can be caused by various dysfunction such as metabolic, cardiac, neurological, infectious condition or tumor progression.¹ From an initial presentation to completed curative cancer patient, the manifestation can occur at any time of malignancy course. Multidisciplinary tumor board discussion is ideal for management optimization.² Radiation is a modality of great use for curative purpose. But for oncologic emergency conditions, there is still much debate among radiation oncologist whether or not urgent administration of radiation is significant for symptoms control.³ Available data are mostly retrospective. It is much subjective among physicians to assess if the delay treatment is going to compromise the outcome. Apart from the usual weekday treatment, some were irradiated during weekends according to retrospective analysis of emergency condition from Canada.⁴ The three most common oncologic emergencies were the following orders: spinal cord compression, brain metastasis and superior vena cava obstruction. Other conditions were acute airway obstruction and uncontrolled tumor hemorrhage.

Brain metastasis

One of the most common cancer metastatic site. There has been increased incidence of brain metastasis with most common primary site of lung, breast and melanoma respectively.⁵ Metastatic cells travel through blood supply to the brain and break the blood-brain barrier. Hematogenous spread tumor is usually found in grey white matter junction with peripheral edema resulting from spherical growing.⁶ Clinical presentation of brain metastasis ranges from occult asymptomatic to neurological deficit. Symptomatic brain metastasis such as headache, weakness, seizure or alteration of consciousness needs urgent treatment to prevent further deterioration, especially the life-threatening increased intracranial

pressure and brain herniation.⁷ Initial corticosteroids (e.g. dexamethasone or methylprednisolone) have been reported to improve brain edema and neurologic deficit up to two thirds of patients.^{8, 9} Available randomized study on dexamethasone regimen given with whole brain radiotherapy reported that initiation of 4 mg is effective in patients without impending herniation. Larger tumor or symptomatic patients may benefit from higher dose such as 16 mg and consider tapering upon dynamic clinical status. In asymptomatic patients undergoing whole brain radiation, corticosteroid can be reserved with close clinical surveillance.

Single brain metastasis

Excluding radiosensitive histology such as small cell lung cancer, leukemia, lymphoma or germ cell tumor, local therapy such as surgery or radiosurgery can be considered in appropriate patients with single or oligometastases¹⁰. Patients with good performance status might be selected for upfront surgery as it can achieve immediate pressure effect relief and definitive tissue diagnosis. After surgery is done, postoperative WBRT is given to increase local brain control at the original site and overall brain metastasis though without survival difference.^{11, 12}

Available recommendation whether or not radiosurgery is comparable to surgery in this setting is largely based on retrospective evidences¹³⁻¹⁶ as most randomized trials were underpowered for conclusions. There is no survival difference between surgery plus WBRT and radiosurgery plus WBRT.

Multiple brain metastasis

Whole brain radiotherapy is considered in brain metastasis with multiple systemic progression, multiple brain metastases, single or oligometastases with large tumor not suitable for radiosurgery, and patient who is inoperable or in poor performance status.¹⁷ However, clinical judgement needs to be reconsidered, especially in poor performance status group, about the risk benefit of radiotherapy.

Recent randomized study¹⁸ found no survival increment combining WBRT with supportive care such as dexamethasone compared to supportive care alone despite minimally increased quality of life.

Treatment consideration

Consensual endpoint such as whether to prioritize brain metastasis control or neurocognition in each patient has to be taken into consideration. However, in an emergency setting, availability of resources and timing of treatment initiation determine the treatment choice.

Target volume definition

Whole whole brain radiotherapy covers the whole skull from vertex inferiorly the field edge line from external auditory meatus to the outer canthus of the orbit with extension 1 - 2 cm lower if there is skull base involvement.¹⁹

For stereotactic radiosurgery, a pathological based study²⁰ found microscopic tumor infiltration in each histology and recommend 1 mm margin added to the visible gross lesion.

Dose fractionation for whole brain radiotherapy

Cochrane review²¹ on available randomized controlled trials reported no significant difference in overall survival or neurological function between different dose regimen; 30 Gy in 10 fractions, 20 Gy in 5 fractions and 40 Gy in 20 fractions twice daily. Update review comparison between 20 Gy in 5 fractions and 40 Gy in 20 fractions twice daily found no survival benefit (Hazard ratio = 1.18, 95%CI 0.89 - 1.56, P = 0.25). No consensus on the dose fractionation of whole brain radiation has been made, however, shorter fractionation with larger dose per fraction such as 20 Gy in 5 fractions or 30 Gy in 10 fraction in edematous brain metastases may result in acute radiation toxicities.²² In patients presented with brain metastases as the initial diagnosis, physician should opt for lower dose per fraction as the disease course might be unpredictable and late radiation toxicity is possible.²³

Spine metastasis

Spinal cord compression may result from primary spine malignancy or metastasis. Most common primary sites are lung, prostate and breast cancer respectively.²⁴ Mechanism of spreading includes hematogenous, shunting of abdominal venous flow to epidural venous plexus and direct neural foramen invasion.²⁵ Early detection of disease preferably before symptomatic is critical for treatment decision. MRI is the modality of choice in evaluation of nontraumatic spinal cord emergencies with sensitivity 93% and specificity 97% in distinguishing malignancy from benign condition.²⁶

In spinal instability, cord compression or neurological deficit at presentation in ambulatory cases should be considered for choice of surgery first²⁷. Indications for surgery include spinal instability, bone impingement from vertebral collapse, previous irradiation given in the area and necessity to acquire pathological tissue.²⁸ In patient who is inoperable or not suitable for surgery such as poor performance status and advance metastasis, radiotherapy is appropriate to palliate symptoms. Apart from surgery and/or radiation, corticosteroid treatment is usually recommended. Despite being such a common medication used in this setting, the data is still vague. Mechanism²⁹ of action is to decrease tissue edema by capillary permeability reduction resulting in a decrease in water content. Steroid-induced hyperglycemia is another mechanism to cause osmotic gradient. High dose steroid and prolong duration of treatment more than 3 weeks³⁰ has been clearly correlated with increased side effect however benefit gain is still controversial.^{31, 32} Further studies are needed to determine dexamethasone regimen for both ambulatory and non-ambulatory patients.³³

The most important prognostic factor to predict post treatment ambulation is pretreatment motor function. Percentage of treatment response between pretreatment ambulatory with or without support versus non-ambulatory group is 97% vs 69% according to studies on vertebral metastatic patient underwent radiotherapy alone.³⁴ Another important decision is timing of radiotherapy. There have still been much debate on the golden hour of surgery in acute spinal cord injury. Prospective study found that early surgery within 24 hours to 48 hours resulted in better neurological function than later than 48 hours although no survival difference was found.³⁵ Retrospective data reported that the nonambulatory patients who completely resumed their motor functions after radiation therapy, the time interval between onset of spinal metastasis symptom and radiation initiation can be up to 10 days.³⁶ Radiation oncologist tend to start radiation early although no consensus has been established. One prospective study found no considerable benefit in neurological outcome when giving emergency radiotherapy within 12 hours to malignant spinal cord compression.³⁷

Radiation technique

Time is the determining factor in emergency radiotherapy setting and this indicate the choice of radiation technique. From historical data, Linear accelerator 6 MV, 10 MV and Cobalt-60 have been used in the treatment. To achieve dose coverage, 3D simulation is planned using either single posterior or parallel opposing fields depending on the depth of spinal cord.³⁸

Target volume definition

Treatment volume is the gross tumor volume plus that whole spinal vertebrae. In 2D using X-ray or 3D using CT simulation planning, the affected vertebrae is treated with two upward and downward extension. When using MRI planning, one vertebra above and below from the affected spine coverage is adequate. In postoperative cases, the tumor bed and orthopedic prosthesis are included.³⁹

Dose fractionation

Various regimen namely 8 Gy single fraction, 20 Gy in 5 fractions, 30 Gy in 10 fractions, 37.5 Gy in 15 fractions and 40 Gy in 20 fractions, had been studied and similar post treatment ambulatory rates were reported.²⁸ Higher dose did not contribute to better functional outcome⁴⁰ while higher fractional dose has been reported to have vascular effect which might lead to cord ischemia.⁴¹ Some studies found that single fraction is associated with higher reirradiation and rate of pathological fractures.^{42, 43} As a result, routine single or hypofraction should be avoided unless in a limited survival time patients.

Superior Vena Cava obstruction

Malignant airway obstruction categorized into upper airway obstruction which can be effectively relieved by emergent tracheostomy and lower airway obstruction which can be assessed and treatment by interventional technique^{44, 45}. While Superior vena cava syndrome or Superior vena cava obstruction (SVCO) is caused by tumor thrombosis within the vein as a result of extrinsic compression or direct tumor invasion. Majority malignancy causes are lung cancers followed by lymphoma.⁴⁶ Diagnosis is usually made by clinical which may present as acute or chronic symptoms depending on degree of SVC narrowing.⁴⁷ There are much controversy whether or not SVCO is considered medical emergency.⁴⁸ Although studies reported that it is not considered direct cause of patient mortality^{49, 50}, their possible life-threatening effects like laryngeal edema or cerebral hypoxia suggesting that one should get immediate attention and appropriate care.⁵¹ Before radiotherapy or other modalities given, there should be attempt to have proper histological diagnosis first⁵². As radiation can result in loss of subsequent pathological diagnosis⁵³. There was no difference of treatment outcome between patient who were admitted and given treatment on weekdays or weekends according to the study from German tertiary care.⁵⁴

Target volume definition

Define the mediastinal mass that caused SVC obstruction on contrast enhanced CT for gross tumor volume. Microscopic margin is added according to pathological type for CTV. And then add setup margin to create PTV.³⁹

Dose fractionation

Although the optimal dose is not yet established, various regimen from single fraction of 6 Gy, hypofraction 3 - 4 Gy for 3 - 5 fractions, 20 Gy or 30 Gy in 10 fractions have been used in historical data.⁵⁵⁻⁵⁷ Symptom relief following radiotherapy were reported from 63% in NSCLC up to 80% in various histology.

Tumor hemorrhage

When encounter the hemorrhage in cancer patient, it can be caused by local tumor vessel invasion and/or systemic coagulopathy. The presentation ranged from occult bleeding to major life threatening event. A retrospective review from single institute⁵⁸ showed that patient who presented with this condition was usually diagnosed of metastatic or locally advanced stage. Various management can be considered for treatment in each patient including dressing, endoscopic embolization, surgery, interventional radiology and systemic treatment⁵⁹. Radiation is considered one of the local modalities to control tumor bleeding. External beam radiotherapy can be applied into many different cancer site such as gastric, uterine cervix, bladder, rectum and skin⁶⁰⁻⁶³. The exact mechanism of how ionizing radiation can stop bleeding is unclear. Possible explanation is that radiation cause endothelial damage of malignant vessels and decrease vascularity⁶⁴.

Radiation technique and target volume definition

Conventional 2D or CT-based 3D simulation is recorded in retrospective data with the use of Linear accelerator for external beam radiation treatment.⁶⁵ Use clinical information combine with contrast enhanced CT to define the gross tumor volume.

Appropriate margin can be added upon physician's discretion. The radiation field aim to cover bleeding tumor burden while limiting dose to adjacent normal organ.

Dose fractionation

Since there is no randomized controlled trial compared between each modalities, it is up to physician's discretion. Retrospective study reported significant improvement of clinical bleeding according to WHO scale in patients with incurable cancer underwent radiotherapy⁵⁴. Various regimen resulted from different clinical cases such as previous irradiation history and chemotherapy treatment. The external beam radiotherapy dose was range from 5 - 45 Gy, median 20 Gy.

Other condition: Cancer pain

Distress from malignant pain requires prompt evaluation. Since pain is multifactorial, complete assessment of disease condition should be considered. A mutual standardized questionnaires is also recommended to assess symptom severity without subjectivity⁶⁶. Necessary diagnostic information such as pathological result is beneficial for radiation response determination⁶⁷.

Target volume definition

Clinical correlation is an important step to identify the pain location especially in diffuse bone metastasis patient who might not tolerate large volume radiotherapy.³⁹ PTV encompass the gross lesion with margin based on setup error and normal tissue sparing modification.

Dose fractionation

To relieve pain caused by bone metastasis, systematic review^{68, 31} found that single fraction of 8 Gy is as effective as multifraction radiotherapy; 20 Gy in 5 fractions, 30 Gy in 10 fractions, 40 Gy in 20 fractions. Pain response rate after radiation was 60.7% with complete pain resolution 23.8% Odds ratio between single and multiple fractions is 0.98 (95%CI 0.95 - 1.02). Similar response was reported in another

systematic review with 59% improvement and 33% complete pain resolution. Odds ratio between single and multiple fractions is 1.03 (95%CI 0.89 - 1.19). However, there was higher re-treatment rate in single fraction group 21.5% vs 7.4% in multiple fractions (Odds ratio 3.44 with 95%CI 2.67 - 4.43). Higher rate of pathological fracture was also higher in single fraction 3% vs 1.6% in multiple fractions (Odds ratio 1.82 with 95%CI 1.06 - 3.11).

Discussion

Early detection of the emergency condition and multidisciplinary tumor board discussion is ideal for management optimization. Prompt treatment is associated with better outcome. External beam radiation therapy is beneficial in terms of alleviate symptom and delay disease progression in various condition with dose fractionation consideration based upon patient performance status and prognosis

Table 1 Summary of dose fractionation in oncologic emergencies.

Oncologic emergencies	Studies	EBRT dose fraction	Endpoint	Conclusion
Brain metastasis	Tsao MN et al.2012 SR 39 trials, n = 10,835	20 Gy/5Fx 40 Gy/20Fx bid 30Gy/10Fx	<ul style="list-style-type: none"> OS (HR1.18, 95% CI 0.89 - 1.56, P = 0.25) Neurologic function 	No difference in altered dose fractionation WBRT.
Spine metastasis	Rades D et al. 2005 Retrospective n = 1,304	8 Gy single Fx 20 Gy/5Fx 30 Gy/10Fx 37.5 Gy/15Fx 40 Gy/20Fx	<ul style="list-style-type: none"> Motor function (26% vs 28% vs 27% vs 31% vs 28%, MVA = NS) Ambulatory status (69% vs 68% vs 63% vs 66% vs 74%, P = 0.578) 2-Year In-field recurrences (24% vs 26% vs 14% vs 9% vs 7%, P < 0.001) 	<ul style="list-style-type: none"> Similar functional outcomes. Less in-field recurrence in multiple fractions.
Superior vena cava obstruction	Armstrong BA et al. 1987 Retrospective n = 125 Sculier JP et al 1986. ⁶⁹ Retrospective n = 643	9 - 12 Gy/3Fx 20 Gy/5Fx 6 Gy single Fx 20 Gy/5Fx 20 - 30 Gy/10Fx	<ul style="list-style-type: none"> Symptomatic relief in 2 weeks between 9-12Gy/3Fx vs 20Gy/5Fx (70% vs 56%, P = 0.09) No comparison 	No difference in altered dose fractionation. Initial chemotherapy due to good response.
Tumor hemorrhage	Cihoric et al 2012 Retrospective n = 62	Range from 5-45 Gy (median 20 Gy)	<ul style="list-style-type: none"> Bleeding control after radiation using WHO bleeding scale (grade 0-4) (p<0.001) 	Radiation is effective for incurable cancer bleeding reduction.

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บทคัดย่อ

บทบาทของรังสีรักษาระยะไกลในภาวะฉุกเฉินทางมะเร็งวิทยา

ปรางระวี แสงจันทร์

รังสีรักษาและมะเร็งวิทยา ภาควิชารังสีวิทยา คณะแพทยศาสตร์ มหาวิทยาลัยธรรมศาสตร์

ปัจจุบันมีผู้ป่วยที่ตรวจวินิจฉัยพบว่ามีภาวะฉุกเฉินทางมะเร็งวิทยาสอดคล้องกับอุบัติการณ์โรคมะเร็งที่สูงขึ้น ภาวะดังกล่าวต้องการการดูแลรักษาภายในช่วงเวลาที่เหมาะสม การวางแผนร่วมกันผ่านการประชุมแพทย์สหสาขาโรคมะเร็งวิทยา จะนำมาซึ่งแผนการรักษาที่สมบูรณ์ทั้งในด้านภาวะฉุกเฉินทางมะเร็งวิทยาและแผนการรักษามะเร็งในระยะยาว ในบางสถานการณ์ที่ไม่สามารถผ่าตัดได้ หรือผู้ป่วยมีสภาพร่างกายไม่เหมาะสมต่อการทำหัตถการที่รุกราน การรักษาด้วยการฉายรังสีระยะไกล มีบทบาทในภาวะดังกล่าว เช่น ภาวะมะเร็งลูกกลมไปสมอง ภาวะมะเร็งลูกกลมไปกระดูกสันหลัง ภาวะหลอดเลือดดำเวโนคาวาอุดกั้น ภาวะเลือดออกจากก้อนมะเร็ง และภาวะปวดจากโรคมะเร็ง

คำสำคัญ: ภาวะฉุกเฉินทางมะเร็งวิทยา, รังสีรักษาระยะไกล