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Mini Review

Adult Palliative Oncology and Radiotherapy of Locally Advanced and Metastatic Cancers

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Abstract

End of life care is perhaps the most challenging in oncology but a learnable skill. Treating patients with advanced and metastatic disease could provide palliation and sometimes may prolong survival. Palliative care is often complex. This paper does not attempt to be comprehensive but attempts to make choices on the best practices in palliative radiotherapy, and will also discuss other palliative modalities. It discusses how to adapt each step of the radiation oncology clinic flow to meet the needs of palliative patients, pain control and the most appropriate techniques in treatment planning and delivery. This paper discusses the most effective and efficient dose fractions for palliative patients. It also discusses some specific challenging scenarios in palliative oncology in selected details hopefully will enlighten. The radiotherapy in palliative cases is different than the curative cases in the intent of cure versus palliation. When active intervention is futile, palliating the pain and suffering of the cancer patient should be the primary treatment goal.

Introduction

End of life care is perhaps the most challenging in oncology [1-8] but a learnable skill [2]. Hospice care is a top priority of the American Society of Clinical Oncology (ASCO), European Society of Medical Oncology, and National Comprehensive Cancer Network (NCCN) [2,9-11]. Palliative care involves compassionate care and meticulous attention to the psychological needs of the patients and their families [2-8]. Radiotherapy is important in palliative care in oncology patients [12]. About 30% of breast cancer patients are diagnosed with stage IV disease [13]. About 50% of breast cancer patients with distant metastasis have radiotherapy as part of their palliative care [14]. Treating patients with advanced and metastatic disease could provide palliation and sometimes may prolong survival [15]. Palliative care is often complex, a multidisciplinary team may be most appropriate [13,16-18].

This paper does not attempt to be comprehensive but attempts to make choices on the best practices in palliative radiotherapy, and will also discuss other palliative modalities. This paper is part of a series [19-27] discussing current challenges of designing radiation treatment target volumes. This paper includes quite a bit of technical details of radiotherapy and the associated local and systemic treatments because the target volumes needed in radiation treatment are intimately related to the treatment techniques being used, and the other treatments the patients receive.

End of life and aggressive treatment

Performance status [28] is a useful predictor of length of survival of cancer patients receiving palliative radiotherapy [29-32]. Patients with poor performance status (Karnofsky Performance Status (KPS) < 60), non-breast and non-bone metastasis [29] have a median survival of 13 weeks, patients with two out of these three poor prognostic factors have a median survival of 29 weeks, and patients with good prognosis survived for a median of 114 weeks [29].

Use of radiotherapy during the last 30 days of life, regarded by many as inappropriate, was 7.6% for top five most deadly cancers lung, breast, prostate, colorectal and pancreatic cancers [29,33]. In another study, aggressive chemotherapy during the last month of life increased the chance of emergency room visit and intensive care unit admission for stomach cancer patients [34].

Simulation and setup

The goal of simulation is to set up the patient in a way that is comfortable and reproducible especially for palliative cases [35-37]. Cancer pain could be aggravated by the daily radiotherapy process (e.g. simulation, immobilization, transportation) and has been undertreated in about 50% of patients [38-40]. During simulation, the iso-center is set usually at the center of the target volume. However, at the treatment machine, when the simulation film is lined up with the port film for low dose CT using bony landmarks, the iso-center may no longer be at the center of the target volume because the position of the target volume is not representative of the average position of the target volume on daily basis [41] possibly due to discomfort of the patient at simulation. This is called the systemic error in addition to the random error due to internal organ motion secondary to respiratory, bowel or bladder filling [42-45]. When system error is large, re-simulation may be required [36,37,41]. Excessively uncomfortable immobilization, especially in palliative cases, may cause pain and discomfort and cause an excessive systemic error in simulation. No correction level of error (typically a few mm) could be applied so that patients need not be moved daily to adjust for minor systemic setup errors [46,47].

Treatment Planning

Familiar with the CT and MRI characteristics of tumors is very useful for treatment planning. CT number is a measure of the tissue density relative to that of water, it could be negative/dark (e.g. air in lung) if the density is lower than that of water [48]. Tumor necrosis is

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a sign of an aggressive tumor [49]. The tumor necrotic center contains largely fluid appears dark on CT [49]. The CT level is usually chosen as the mid value of the CT numbers, and CT window is the range of CT numbers to display [48]. For high resolution imaging, an entire volume of tissue could be imaged to multi-slice CT that acquires all the slices in one revolution as opposed to acquiring each slice one at a time and reconstructs the volume leading to reconstruction artifacts [48]. See [50] for a very useful online reference for tumor imaging.

For brain tumor imaging [50,51], it is useful to note that fat is dark on CT (- 100 HU), bright on both T1 and T2 MRI [50]. Extra-cranial tumors (about 80% are meningioma and schwannoma) or arise from outside the brain or its coverings, intra-axial tumors are mostly (about 75% are metastasis or astrocytoma) [50]. Extra-cranial tumors do not have blood brain barrier (BBB) so the contrast enhances homogeneously, with a broad dural base and a dural tail of enhancement [50]. The dural tail is not part of meningioma, and needs not to be treated routinely unless there is a radiographic evidence of invasion [52]. Meningioma, glioblastoma multiforme (GBM) and radiation necrosis (appears similar to GBM) could cross the midline, and multiple sclerosis (MS) could present as single or multifocal masses [50]. Radiation brain necrosis shows finger like edema on T2 MRI and heterogeneous gadolinium enhancement on T1 MRI with contrast after the necrosis liquefies [53,54]. Brain tumors, infarction, infection or demyelinating disease (MS) that destroy the BBB, and pituitary and pineal glands that do not have BBB will enhance with contrast [50]. Pituitary stalk runs at an angle inferiorly to the pituitary gland [50], similar and close to the optic path. The brain tumor and normal tissue interface usually appears differently with different imaging modalities [50,51,55]. The volume of brain tumor imaged by T2/FLAIR could be larger than T1 with contrast MRI [56]. Contrast enhanced CT in the arterial phase clearly delineates the margin of hepatocellular carcinoma [57,58]. Multimodality imaging may be needed for accurate (not under or over covering) target delineation using the composite image [55,56].

Contouring of brain target and normal tissue volumes is best performed in multi-planes. The contouring is not purely anatomical, but also biologic and clinical (considering, for example, the performance status and concurrent chemotherapy). Pre-planning of the treatment volumes (target and normal tissue volumes) is useful.

Dose and fractionation

A protracted course of many weeks may not be the most effective ways for the patients to spend their last few months [35]. A typical hypo-fractionated palliative dose is 3000c Gy in 10 fractions and is highly effective, especially with concurrent chemotherapy [31,59,60]. In this case report, 30 Gy in 10 fractions was used with nedaplatin (80 mg/m2 (day 1)) and 5-fluorouracil (800 mg/m2 (day 1-4) [60]. The patient continued with chemotherapy and had 17 months of local control of 3.9 x 3.5 cm lower esophageal squamous carcinoma [60]. In this study, 6 Gy once a week for 5 weeks was used to treat a very advanced squamous cell skin cancer with good pain control [35]. Other dose fractionation could very from 8 Gy x 1 for a simple bone metastasis, to 4 Gy x 5 fractions for different sites, 8.5 Gy x 2 fractions for lung cancer, and 2 Gy x 23 fractions for many sites [12,31]. Very high dose per fraction has high risk of radiation side effects, for example, 8 Gy x 1 has more risk requiring re-treatment [61], and injury from the re-irradiation and pathologic fracture [12]. Periosteal edema could happen in about 40% of patients with bone metastases receiving 8 Gy x 1 radiotherapy requiring more analgesic use [62,63]. This could be rescued by 8 mg dexamethasone for 1 to a few days [62-64]. 1700 cGy in two fractions over 3 days provided about 70% relief from hematuria and about 50% relief from pain [65]. The older hypo-fractionated high dose regimens should be used for patient with very limited life expectancy less than one year [12,65,66].

Pain control

Pain control is a very important but sometimes ineffective area in palliative care [67]. In South Korea, it is estimated about 60% of cancer patients experience cancer pain, 90% of cancer pain is controllable, however, cancer pain is undertreated in about 40% of patients [67]. This under-treatment is related to oncologist's poor knowledge of using opioids and alternative pain control methods, exaggerated fear of opioid addition and fear of respiratory suppression [67,68]. World Health Organization (WHO) has published a widely used pain control ladder for pain control in patients with advanced cancers [69,70].

Neuropathic pain includes somatic pain that is sharp (e.g. from cutting) versus visceral pain (e.g. from distention and ischemia) that dull and arching [71]. Radiotherapy and analgesic are important components in cancer pain control [72,73]. Mild pain could be treated with non-steroidal anti-inflammatory drug (NSAID) and paracetamol [72,74], moderate pain could be treated with mild narcotic (e.g. codeine, tramadol, dextropropoxyphene) [72] and severe pain could be treated with morphines [72]. Neuropathic pain could also be treated with anticonvulsant gabapentin and tricyclic anti-depressants [72] and steroid [75].

Bone metastasis

For patients with spinal metastasis, radiotherapy is a standard of care treatment, it provides about partial pain relief in about 60% and complete pain relief in about 30% patients [12]. Patients with spinal metastasis could also be treated with vertebroplasty and kyphoplasty [12]. Bone cortex and marrow have no nerve endings [72,73]. Neuropathic [76] bone pain from metastatic disease could be caused by fracture, irritation of periosteum and endosteum, nerve root compression and muscle spasm [72]. Treatment of bone metastases related event is about US $28000 and treatment coats about US $10000 per patient [72,77]. Bone fracture is the most common event related to lytic bone metastasis [77]. CT long bone cortical involvement of more than 30% should be considered for prophylactic fixation prior to radiotherapy [78]. Zoledronic acid was the first bisphosphonate used to treat bone metastasis and strengthen the bones [72]. Bisphosphonates such as Aredia could relieve malignant bone pain in 50% of patients [72,79]. Bisphosphonate inhibits osteoclast activity and could impair bone integrity and bone healing [80]. Bisphosphonate related mandible (maxilla less commonly) necrosis could be confused with metastatic disease that include PET avidity, tissue sclerosis and stranding [80].

Lung cancer

For patients with large lung cancers, radiotherapy is largely palliative [81]. When the tumor is larger than 7 cm, chemotherapy (four courses in 3-week intervals: intravenous carboplatin with area under curve of 5 [81,82] on day 1, oral vinorelbin 0 mg/m2 days 1

and 8) and radiotherapy (hypo-fractionated 42 Gy/ 15 fractions) improved overall survival from 9.7 months to 13.4 months compared with chemotherapy alone [81]. The patients received chemotherapy first and needed radiotherapy was treated with 17 Gy over 2 fractions [81].

About a third of lung cancer patients have hypercalcemia especially patients with squamous cell lung cancer [77]. Hydration, diuretics (40 mg furosemide IV every 12 to 24 hours), glucocorticoid (60 prednisone orally daily or 100 mg hydrocortisone IV every 6 hours), IV bisphosphonate normalize malignant hypercalcemia in most patients [77]. Bronchial obstruction could be relieved by endoscopic cryotherapy [83] and radiotherapy.

Triple negative breast cancer

For triple negative (ER (estrogen receptor) negative, PR (progesterone receptor) negative, Her2 (human epidermal receptor) negative), estrogen receptor alpha targeted therapy has been used to treat patients with triple negative metastatic breast cancer [84]. One of its major side effects is cachexia secondary to loss of nutrient sensing and metabolism leading to muscle wasting and fatigue [84].

Stomach cancer

In one study, 30 Gy in 3 Gy fractions provided about 70% relief from blood transfusion from gastric bleeding for more than a month [59], about 50% of the patients developed rebleeding [59]. The median time to rebleeding in the study was 3.3 months [59], and patients received concurrent chemotherapy had lower rebleeding rate [59]. Bleeding from stomach melanoma been treated with more hypofractionated16 Gy in 4 Gy fractions that provided 4 months of relief, and could be retreated with 9 Gy in 3 Gy fractions in this case report [85] . In this study, a median dose of 35 Gy in 14 fractions to the stomach provided control for bleeding, dysphagia/obstruction and pain in about 70-85% of patients [86], and control for the remaining part of life in about 50% of these patients [86]. A biological equivalent dose (BED) of equal or more than 41 Gy was found to be needed for good control of gastric symptoms [86].

Colorectal cancer

For colorectal cancer patients, obstruction and perforation is usually managed by colonic resection, stoma, lavage, internal bypass or stenting [18]. Bleeding, pain or tenesmus and fullness could be managed by radiotherapy [18].

Brain and brainstem metastasis

Radiotherapy Oncology Group (RTOG) performed a trial comparing whole 5 x 4 Gy versus 15 x 3 Gy or 20 x 2 Gy, the survival was the same using the shorter or the longer courses of radiotherapy [30]. The risk of neurotoxicity was higher with the large dose pre fraction whole brain radiotherapy [30].

Brain stem metastasis is challenging to treat because it is located in the critical area [87-89], brain stem metastasis less than 1 ml may be safely and effectively treated with Gamma Knife stereotactic radiosurgery with a median dose of about 16 – 18 Gy prescribed to 50% [87-89]. For larger brain stem metastases or patient received whole brain radiotherapy, they could be treated with 21 – 30 Gy in 3 -5 fractions [88]. In this study, MRI T1 with gadolinium contrast was used to define the target; no clinical margin was used [88]. Six months survival after Gamma Knife SRS (minimum of 16 Gy) was 42%, with shorter survival for patients also received whole brain radiotherapy (3750 cGy whole brain followed by 16 Gy or less SRS boost) in this study [89]. Neurocognitive function is worse after whole brain and SRS when compared with SRS [90]. Upfront SRS for solitary or limited brainstem metastasis may be the better treatment saving the whole brain radiotherapy for salvage [91] in palliative cases.

Conclusion

The radiotherapy in palliative cases is different than the curative cases in the intent of cure versus palliation. When active intervention is futile, palliating the pain and suffering of the cancer patient should be the primary treatment goal.

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