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Role of Radiotherapy and Chemotherapy in the Management of Spinal Cord Tumors

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Abstract:

Spinal cord tumors are either primary or metastatic with 5 percent intra medullary and 90 percent in epidural. These are symptoms such as sphincter dysfunction, motor and sensory deficiency and pain. Pain aggravates overnight and may result in the total spinal cord transection syndrome. Depending on the in-growth of the tumors (metastatic epidural tumors), they can cause root pain, bowel and bladder disorder, unsteady gait as well as paraplegia or paraparesis. This paper compares the outcome of immunotherapy, chemotherapy and radiation to patients with malignancies on the spinal cord. Concentrating on patient history, tumor characteristics, and therapy administration, the survey assesses the effectiveness of different treatment methods in the context of neurological consequences, toxicity rates, survival rates, and local disease control by using sources including PubMed and Google Scholar. The findings of all the articles brought the idea that surgical resection is, indeed, the aim of care, and in most cases, extra adjuvant treatment involves chemotherapy with radiation therapy, depending on the pathogenesis of the tumor and its specific reasons. Also, progressive-free survival is shown to lengthen with radiotherapy and surgery in isolated cases, and radiotherapy and chemotherapy combined are shown to stabilize recurrent ependymomas. Nevertheless, the effectiveness of chemotherapy in the treatment of certain cancers, e.g. astrocytoma is doubtful. The situation is altered by new techniques that have demonstrated outstanding results as regards local control with minimal toxicity such as carbon-ion radiotherapy, stereotactic radiosurgery, and additional radiations therapy. New chemotherapeutic agents, Dordaviprone (ONC201) in patients and in H3 K27M-mutant diffuse

glioma, which is an untreatable cancer with only the radiation therapy option to rely on.as summary of the trials is to come up with a protocol to avoid neurological impairments and surgical difficulties because an incision of the chord may ruin columns to the spinal cord. Even in this progressive situation, the best treatment for spinal cord tumors is still unclear so, it needs more studies in large populations and prolonged duration and to compare advantages and disadvantages of all interventions to establish definitive management paths.

Keywords: spinal cord tumors, stereotactic radiosurgery, H3 K27M-mutant diffuse glioma.

Introduction

Spinal cord tumors can be divided into primary and metastatic, based on which cells these tumors originated. Each of them can be located in extradural, intradural extramedullary and intramedullary spaces. Approximately 90 % of spinal tumors are metastatic epidural tumors (1). In contrast, intramedullary primary spinal cord tumors are rare and make about 5 % of tumors affect the central nervous system (2). In adults, the most frequent intramedullary spinal cord tumors are Ependymoma (60-70%), Astrocytomas (20-30%), Other less common tumors such as metastases, lymhoma and lipomas, in children astrocytomas and gangliogliomas are more frequent (3). The clinical presentation of spinal cord tumors varies, based on where the tumor is located, which part of spinal cord is disrupted. Commonly most expressed symptom of expressing is pain, which may worsen at night and can be reinforced by actions such as coughing, sneezing or straining (2). Intramedullary spinal cord tumors typically present with pain, motor and sensory impairments and sphincter dysfunctions. Symptoms usually progress gradually and can eventually lead to complete spinal cord transection syndrome (4). Metastatic epidural tumors, due to spinal cord compression, may present the following clinical features Radiculopathy-characterized by radiating pain, along with sensory and motor deficits in the affected nerve distribution, Bladder and bowel dysfunction, Gait instability, Paraparesis or paraplegia (5). Nowadays, preferential treatment for intramedullary tumors relies on surgical resection, especially for well-circumscribed lesions, but for incompletely resected, surgically unresectable tumors, high-grade tumors or recurrent tumors radiation therapy and systemic treatment can be indicated (2). Research has been done to assess the effectiveness treated and the safety of radiotherapy, stereotactic radiosurgery and also the chemotherapy that are given to various spinal cord tumors.

Stereotactic radiosurgery can be alternative or adjuvant treatment to surgery for benign spinal tumors including meningiomas, schwannomas and neurofibromas (6). Stereotactic radiosurgery delivers the lethal does to a target within spine with sub millimetric accuracy (6). Stereotactic irradiation for spinal cord metastasis can be recommended in case there are unadvisable surgical methods and chemotherapy for this pathology (7). Action is an international, randomized, doable-blind, placebo controlled, phase 3 trial of ONC201 in adult and pediatric patients with H3 K27M-mutant diffuse glioma was designed to assess efficacy of ONC201 (dordaviprone) against H3 K27M-mutant diffuse glioma, because there

exist no effective treatments other than radiation and a median overall survival of approximately 1 year (8).

In addition, Tumor appearance, Intervention details, Outcome measures include local control rates, fusion success rates, neurological status, survival rates, and side effects. Follow-up duration. Imaging and evaluation criteria Furthermore, as and when needed, information was collected about the study design, sample size, treatment protocol, and statistics used (3).

Treatment Modalities and Protocols:

1) Surgery: Open resections and spinal stabilisation procedures were some of the surgeries. The general health of a patient, neurological status, and resectability of the tumour would typically be considered in determining eligibility for surgery.

2) Radiotherapy: Both conventional radiotherapy and newer methods such as proton therapy, stereotactic body radiotherapy, and stereotactic radiosurgery were included. Dosage and fractionation regimens varied; some employed conventional fractionation, while others indicated high-dose radiation. When radiotherapy was mentioned in addition to surgery, it was noted whether it was pre- or post-surgery.

3) Chemotherapy and Immunotherapy: Chemotherapy regimens varied according to tumour type and included systemic agents with known activity against gliomas or metastatic disease. Less frequently, immunotherapy was reported, preclinical data offer hope for tumour control and osteogenesis, but with less clinical proof currently.

4) Osteobiologic Agents: Spinal fusion patients were evaluated for a variety of osteobiologic materials, including growth factors, autografts, allografts, demineralized bone matrices, and biomaterial scaffolds. Their effect on fusion rates and equipment stability was considered, with particular attention to added radiation and chemotherapy (5,6).

Developing such method would prevent surgical complications such as neurological deficits. Tumor-induced changes in the spinal cord can make midline difficult to detect, and a myelotomy on the posterior surface of the cord can injure the posterior columns or compromise the spinal cord blood supply (4).

Method

The aim of this Narrative review is to compare the effects of various medical treatments, including radiotherapy, chemotherapy, and immunotherapy, on patient outcomes in various spinal and intracranial neoplastic diseases. They include metastatic spinal disease, spinal metastases from hepatocellular carcinoma, benign spinal tumors, intramedullary metastases, and pediatric low-grade gliomas in the spinal cord. This review critically evaluates the effectiveness of these treatments, local

control rates, survival rates, neurological function, and toxicity profiles of these medical interventions (1,2,3)

Literature Search Strategy: A literature review of databases, including PubMed, Google Scholar, was conducted to look for pertinent research studies published until this date. The search keyword entails terms such as spinal tumors, gliomas, metastases, stereotactic radiosurgery (SRS), stereotactic body radiotherapy (SBRT), proton therapy (PT), osteobiologics, chemotherapy, immunotherapy, surgery, and corresponding outcome measures. To achieve completeness, the reference lists of the pertinent articles and reviews were also carefully evaluated.

Inclusion and Exclusion Criteria

Inclusion Criteria: Spinal tumors or metastases and hepatocellular carcinoma with spinal involvement in patients. Surgical resection, chemotherapy, radiotherapy, immunotherapy, and osteobiologic agents are some of the techniques used in spinal fusion or tumor treatment. Research on local tumor control, neurological function, fusion rates, survival, side effects, quality of life, and functional ability. Cohorts and case series, case reports, and clinical trials. The study considered both adults and children. Articles are in English, which is a requirement.

Exclusion Criteria: Studies that did not have individual patient data, studies with fewer than five patients if new information was not presented, and studies that did not involve humans were excluded.

Data Extraction: We extracted data from studies that met the criteria for consideration of the following factors: Information on the age, sex, and other demographic features of the patient.

DISCUSSION

Due to their peculiar and varying presentation, Spinal cord tumors pose a significant therapeutic challenge leading to constant advances and research in the direction of improving the current treatment regimens. Amongst these, the rarer intramedullary tumors present a bigger challenge because surgery for them has a higher risk of damage to the spinal cord tissue and are often infiltrative, this gives them a higher potential of causing permanent neurological deficits. Naturally, in the literature reviewed, there has been a higher focus on advancing the treatment of intramedullary tumors in recent times. The mainstay of the treatment remains surgical resection (2). Although, according to differing protocols and indications, adjuvant radiotherapy and chemotherapy are added often. Direct indications, implications and specific benefits of treatment vary with tumor etiologies and must be studied accordingly.

The first way in which radiotherapy can be integrated into the treatment regime is its usage as an adjuvant to the surgical procedure, while Radiotherapy and Chemotherapy without surgery seems to be reserved for those patients in whom the tumor appears inoperable due to infiltration, radiosensitivity etc, where preserving neurological function takes priority (2). The literature reviewed all through-out shows relatively better prognosis in cases where adjuvant radiotherapy is considered. In cases of intramedullary ependymomas, indications for adjuvant radiotherapy (RT) depend on the

WHO Grade of the tumor and the extent of resection post-surgery which is determined by a post-surgery MRI (5). Adjuvant radiotherapy is indicated in Grade 2 tumors with incomplete resection, a focal radiotherapy (of 45-54 Gy) is shown to improve progression-free-survival (PFS) in Grade 2 tumors where resection is not possible.6 In Grade 3 and 4 tumors regardless of extent of resection, adjuvant chemotherapy is indicated because of their highly proliferative and infiltrative nature (3). For Intramedullary Astrocytoma of WHO grade 3 and 4, postoperative fractionated radiotherapy is recommended regardless of the extent of resection. Radiotherapy is additionally indicated for biopsied unresectable IMA or in case the tumor progresses after surgery (4.) Various studies suggest longer overall survival after radiotherapy in patients with high-grade intramedullary astrocytoma (4).

As in any other treatment regimen, Radiotherapy is not always deemed to be free of side-effects. The spinal cord's radiation dose tolerance is reported to be approximately 50 GyE, exceeding which makes the patient prone to late radiation myelitis, causing irreversible tetraplegia or paraplegia (9). To improve prognosis further, others advocate the usage of a combined radio-chemotherapy either with or without preceding surgery. The studies reviewed show both an advantage and a shortcoming of this approach, primarily differing with the etiology in consideration. For instance in cases of recurrent ependymomas, chemotherapy with temozolomide (TMZ) is considered even though its efficacy is deemed questionable, alone or in combination it has shown stable disease in 36-50% of patients with an average progression-free-survival of 2-10 months (TMZ in isolation as well as in combination has been proven to stabilize disease in a considerable percentage of patients with recurrent ependymomas(2). A combination of chemotherapy and radiotherapy is also considered in comparatively complicated High-Grade Astrocytomas with Piloid Features (Postoperative RT + TMZ /BRAF, MEK, or FGFR inhibitors), Spinal Glioblastoma IDH wildtype (post-surgical Focal RT +/- chemotherapy; MZ for progression), Spinal Glioblastoma (post-surgical RT + TMZ), Myxopapillary Ependymomas (Postoperative RT; TMZ for prolonged disease control) (2).

However, a lot of the data for the role and efficacy of chemotherapy for spinal ependymomas comes from studies before the WHO 2021 classification, which makes it somewhat unreliable, the lack of clear data to guide the choice for first-line drugs of spinal ependymomas worsens the implementation (2).Despite the questionable efficacy, for high-grade tumors, histological diagnosis via biopsy followed by combined radio-chemotherapy is perhaps the most common treatment protocol,5 primarily because there is considerable evidence to substantiate the fact that Chemotherapy adds a valuable efficacy when used as an adjuvant. Another undeniable advantage of adopting a chemotherapeutic agent in the treatment protocol is that it offers a well-rounded, systematic approach which can potentially prove beneficial for better management of metastatic diseases.

Although, a fact that limits the implementation of chemotherapeutic agents is that the toxic effects of these drugs are plenty and they can be intolerable for some patients, especially those with intramedullary spinal cord glioma.1 Additional to a lack of widespread studies, many remain against efficacy of adjuvant chemotherapy. One such etiology is spinal cord astrocytoma, where despite the presence of some favorable evidence, the efficacy of chemotherapy remains controversial, and the

indication thereof is not recommended widely (10). The lack of focused studies regarding many tumors and chemotherapeutic agents make the usage even harder, for example, the efficacy of platinum-based regimens cannot be undeniably proven because the studies include a mix of studies for intra-cranial and spinal tumors (2). An interesting case of this nature, where a consensus amongst literature is missing, is of Pilocytic Astrocytoma (PA). On one hand, adjuvant RT is of debatable efficacy with a few retrospective series even indicating a lower PFS with adjuvant RT. The recommendation in this case for prolonged disease control includes chemotherapy combinations including TMZ, carboplatin, vincristine or bevacizumab (2). On the other hand, some studies like the ones retrospectively showing worse outcomes associated with chemotherapy usage in spinal pilocytic astrocytoma (which may be unreliable due to selection bias) make the implementation somewhat questionable (2).

In recent times, owing to the advances in classification and detailed description of various Spinal Cord tumors, novel approaches regarding their treatment regime have gained significant momentum and show promise towards increasingly effective methodologies. Microsurgery is one such novel approach with increasing implementation. For Hemangioblastomas, the tumors are resected using a specialized microsurgical technique where the arterial feeders are coagulated and tumor capsule is dissected to achieve a “en bloc” resection (3). When surgery is not possible, one turns to Stereotactic radiosurgery (SRS) or fractionated RT (2). These Stereotactic approaches mentioned here constitute a novel branch of procedures that have been made possible due to significant advances in the science and technology of both imaging and radiation therapy.

Stereotactic approaches involve the use of high dose radiation in spinal cord tumors to a highly localized (often with the use of CT/MRI) target. Stereotactic radiosurgery (SRS) comprises of highly accurate use of lethal high dose radiation to such an extremely localized target in the spine (6). Other stereotactic procedures are Stereotactic High Dose Irradiation (SHDT) and Stereotactic Body Radiotherapy (SBRT) where the high-dose radiation is used multiple times. These have shown promising outcomes with local control rates of 76-100%, with even higher local control rates for specific lesions including 98%, 95% and 88% at 3, 5 and 10 years for meningiomas, schwannomas and neurofibromas respectively (6). This technique has been advocated also an adjuvant to surgery in cases of subtotal resection or recurring lesions of benign spinal tumors, they even show promise as means of symptom control for example as a pain management in benign spinal tumors (6,7,11).The studies present these modalities as safe, effective, side-effect free and time efficient treatment options for Intramedullary Metastases (7,11). When considering the limitations on the other hand, the highly technical aspect of this modality necessitates a multi-disciplinary approach limited to specialized centers, making its implementation limited, furthermore what complicates the procedure is the requirement for highly accurate delineation of the adjacent OARs (6). Limiting its indications further is the fact that there is a definite lack of studies, wherein currently there are a limited number of studies and even those focus only a certain number of tumors. Radiation-induced Myelopathy (RIM) is also a potential rare complication of stereotactic procedures which is dependent on technicalities like radiation dose, fractionation, length of the exposed part of the spinal cord, and treatment duration (6,7). This solidifies the importance of technical expertise and nuances in these procedures.

Other areas of advancement include the management of Primary Malignant Spinal Tumors (PMST) and Metastatic Spinal Tumors (MST), where the advancement ranges from better diagnosis (imaging and histology) to better treatment including advancements in resection, radiation and chemotherapy (9). Particularly of note, is a novel approach in the application of heavy particle therapy specifically in the form of carbon-ion radiotherapy (CIRT). Characteristic of this radiotherapy is a phenomenon called Bragg Peak, where CIRT delivers large doses of radiation to the target with very little radiation being dissipated from any other site (9). Another novel therapy was suggested by a study that suggested proton therapy (PT) for favorable long-term outcomes in pediatric patients with spinal low-grade gliomas. (12). The freedom-from-progression and OS reported in this study were 73 and 55% respectively. The study argues that PT could potentially be developed as first-line treatment in these patients (12). Just as radiotherapy, chemotherapeutic approaches also are advancing at an appreciable pace with novel approaches being developed and highlighted time and again. An example is ACTION, an ongoing Phase 3 randomized, double-blind study of a dopamine D2 receptor antagonist drug dordaviprone (ONC201) in newly diagnosed H3 K27M-mutant diffuse glioma patients who have undergone standard frontline radiotherapy (8). This is an important endeavor as this specific tumor currently has no effective treatment other than radiation and a median overall survival of approximately 1 year. The success of this trial potentially leads to regulatory approval (8). Additionally, there is a myriad of novel chemotherapeutic agents being suggested for the treatment of different etiologies. These include Belzutifan (a HIF-2a inhibitor) for VHL-related hemangioblastomas; brigatinib, neratinib and selumetinib for NF2-associated progressive tumors; antibody-drug conjugates targeting HER2 in spinal ependymomas (due to a high HER2 expression in the tumor.6 Newer BRAF antagonists are even showing better efficacy in PAs with a BRAF fusion and are potentially a promising alternative for recurrent and unresectable Pas (2).

As is evident, there still seems to be a debate and a lack of consensus over much of the implementation of both Radiotherapy and Chemotherapy in Spinal Cord Tumors, whether it be as adjuvant or as an isolated agent across numerous etiologies. This is partly due to the rarity of some, there are no satisfactorily good treatment (or even sometimes diagnostic) standards to follow, an example is of spinal cord gliomas (13). Even for spinal astrocytoma, the optimal classification and treatment protocols remain to be established with a proper consensus (2). Small sample sizes and a lack of long-term follow-up were observed across all the literature reviewed. Additionally, there is a significant need for prospective studies as opposed to retrospective to accurately track and clarify the roles of various RT and chemotherapeutic treatment regimens. When considering SRS and other Stereotactic approaches, there is an evident lack of studies drawing comparisons with surgeries for varied tumor types. Another major gap seems to be lack of data regarding long term effects as many of the studies reviewed faltered in accordance with long-term follow-up. The most major gap that is evident is the absence of clear and optimized management algorithms applying radiotherapy and chemotherapy effectively (13).

Conclusion

The aim of this study is to evaluate effectiveness of combined roles of radiotherapy and chemotherapy (along with surgical resection of the tumor), while also including advanced and specialized treatments or technologies which can help promote healing, reduce pain and can extend beyond basic treatments for patients with spinal cord tumors. Intramedullary spinal cord tumors (ISCT's) are a heterogenous group of rare neoplasms which require versatile approach and continuous research to see much improved outcomes. Surgical resection with postoperative radiotherapy has shown significant neurological recovery and a decrease in the recurrence of tumors, thus showing better results as compared to when surgery is considered as treatment alone.

For spinal cord astrocytoma's, clinicopathological characteristics and the prognostic values can provide valued information for evidence-based management. As ISCT's are a rare and slow progressing tumor, expert centers with access to latest technical advances and multidisciplinary input are necessary. Early detection is crucial and with recent advances in imaging, early detection as well as precise and advanced treatment plans have improved quite significantly, using newer techniques such as functional MRI, diffusion weighted imaging and hybrid modalities like PET-CT and PET-MRI, as detailed anatomical and functional insights are given with the cooperation of different domains like the radiology, surgery and oncology departments, we have seen a much-enhanced expansion of management strategies for spinal tumors. To standardize treatment protocols, conducting molecular studies with international researchers for these tumors is essential. A good example is the ACTION trial, which assessed the safety and efficacy of ONC201, which can help validate treatment for patients diagnosed with H3 K27M-mutant diffuse glioma, if proven effective, can be implemented in multiple countries.

Osteobiologics when combined with surgery, looks promising but still need proper evidence to prove its efficacy, especially when combined with either radiotherapy or chemotherapy. Radiotherapy still will continue to play a major role in the treatment of both benign and malignant tumors. Stereotactic radiosurgery (SSRS) and stereotactic body radiotherapy (SBRT) have proven to be safe and effective form of treatment in mindfully selected cases like patients with benign tumors and intramedullary metastases. SSRS is performed as alternative treatment to surgery in selected patients with medical comorbidities and SBRT is used as an effective and rapid treatment option for palliative patients. In case of Intramedullary Metastases (IMM) where surgery is contraindicated, high-dose irradiation is used as a safe, effective and time-saving treatment.

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