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Palliative Radiotherapy in Gall Bladder Cancer - A Concise Review

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ABSTRACT

Palliative radiotherapy effectively manages symptoms like pain and bleeding in gallbladder cancer patients. It offers localized treatment, minimizing systemic side effects, and can be combined with chemotherapy for enhanced symptom control. Radiotherapy provides targeted relief for specific tumor-related complications, improving quality of life for individuals with advanced gallbladder cancer. This review summarizes the role and benefits of palliative radiotherapy in managing this challenging disease, focusing on its symptom-directed application and potential integration with other treatment modalities.

INTRODUCTION -

Gallbladder cancer carries a grim prognosis, characterized by disappointingly low 5-year survival rates. This unfortunate outcome is primarily attributed to the aggressive nature of the disease, which exhibits high rates of both locoregional recurrence, where the cancer returns near the original site, and distant metastasis, where cancer cells spread to remote organs. The challenges in early detection and the limited effectiveness of current treatment options further contribute to the poor long-term survival prospects for individuals diagnosed with gallbladder cancer(1).

Palliative radiotherapy plays a significant role in the management of gallbladder cancer, offering crucial symptom relief for patients facing this challenging diagnosis. It is not intended to cure the cancer but rather to improve the patient's quality of life by addressing specific symptoms.

Pain, often severe and debilitating in advanced gallbladder cancer, can be significantly reduced through targeted radiation therapy. The mechanism of pain relief involves shrinking the tumor, which reduces pressure on surrounding nerves and tissues. Bleeding, another potential complication of gallbladder cancer, can also be controlled with radiotherapy. The radiation can damage the blood vessels supplying the tumor, thereby decreasing blood flow and mitigating hemorrhage.

Obstruction, whether in the bile ducts or the gastrointestinal tract, can be alleviated by radiotherapy shrinking the tumor mass that is causing the blockage. This can improve biliary drainage and restore some degree of normal digestive function(2,3,17)

Advanced stages at diagnosis often involve extensive local spread and involvement of critical adjacent structures, making complete surgical removal difficult. Moreover, the propensity for distant metastasis, particularly to the liver, lungs, and peritoneum, significantly reduces the chances of long-term survival (4).

The specific radiation dose and treatment schedule are tailored to the individual patient's needs and overall condition, balancing the benefits of symptom relief with the potential side effects of radiation. Furthermore, palliative radiotherapy can be combined with other treatment modalities, such as chemotherapy or pain management strategies, to provide a comprehensive approach to symptom control

and improve the patient's overall well-being. The decision to utilize palliative radiotherapy is made in consultation with the patient and their healthcare team, taking into account the patient's individual circumstances, the extent of the disease, and their overall goals of care(5,6).

Gallbladder carcinoma (GBC) is an aggressive malignancy; surgical resection is the only curative treatment(7). Loco-regional failure is the predominant pattern, followed by systemic failure. Adjuvant radiotherapy has been used with concurrent and adjuvant chemotherapy to improve survival. Retrospective studies show improved survival with adjuvant radiotherapy in patients with regional spread or liver infiltration(8).

Modern radiation techniques may improve outcomes without increasing toxicity. Simple cholecystectomy is adequate for T1a tumors; extended cholecystectomy is recommended for others. Achieving R0 resection is crucial for improving survival; adjuvant therapy is logical for better tumor control. Studies show varied results on the benefit of adjuvant radiotherapy after R0 resection; some show improved survival, others do not. Concurrent chemotherapy, especially with fluorouracil or capecitabine, is recommended with adjuvant radiotherapy.Newer techniques like IMRT and image-guided radiotherapy may optimize dose delivery and minimize morbidity(6,7).

EMERGING ROLE OF RADIOTHERAPY IN PALLIATION

Khatri et al.(9) in a retrospective study compared best supportive care (BSC) with chemotherapy (GEMOX) and/or radiotherapy in unresectable gallbladder cancer. The study included 50 patients divided into three groups: BSC, GEMOX chemotherapy, and GEMOX with radiotherapy. While no statistically significant difference was found between groups, GEMOX with radiotherapy showed improved progression-free survival in some patients.

Sinha et al.(10) in a Randomised study analyzed 45 patients with unresectable, non-metastatic locally advanced gallbladder cancer. Twenty patients received only chemotherapy, while 25 received radiotherapy(45–50 Gy at 1.8–2 Gy per fraction) with concurrent chemotherapy. Two-year progression-free and overall survival rates were significantly better in the radiotherapy group. Locoregional progression was more common in the chemotherapy-only group (85% vs 32%). Radiation-induced toxicity was generally mild, with only a few patients experiencing grade 3 or higher side effects. Adding radiotherapy to chemotherapy improves survival outcomes in these patients. The study suggests that chemoradiotherapy should be considered a standard treatment option.

Sekar et al. (11) in a randomized controlled study compared chemotherapy and radiotherapy in advanced gallbladder cancer. Patients were randomly assigned to chemotherapy or radiotherapy groups. Symptomatic response was higher in the chemotherapy group (80.7%) than the radiotherapy group (61.4%). Overall response rate was better with chemotherapy (38.4%) compared to radiotherapy (26.8%).Median progression-free survival was longer with chemotherapy (7.24 months) than radiotherapy (6.11 months). Both treatment groups had similar baseline characteristics. This study showed that Chemotherapy showed superior response rates and survival outcomes in advanced, inoperable gallbladder cancer.

Gallbladder cancer has a low 5-year survival rate due to high locoregional and distant failure rates(12).

In a study published by Engineer et al.(13) ,Locally advanced gallbladder cancers (stage III) with poor prognosis were treated with neoadjuvant chemoradiation. 28 patients received concurrent chemoradiation using helical tomotherapy and gemcitabine. 25 patients completed the chemoradiation, with 20 achieving partial or complete response. 18 patients underwent surgery, 14 achieving R0

resection (complete removal of tumor). Median overall survival was 20 months; 5-year OS was 24% (47% for R0 resection). Common side effect was biliary leak (43% of surgical patients), requiring intervention in two cases. Neoadjuvant chemoradiation may improve outcomes for locally advanced gallbladder cancer, facilitating curative resection.

A prospective study by Gupta et al.(14) involved 62 patients with unresectable advanced gallbladder cancer. Pain was the most common symptom (92%), followed by obstructive jaundice (46.7%). Palliative treatments included percutaneous biliary drainage, stenting, ascitic tapping, and pain management. Palliative chemotherapy was considered for patients with good performance status. The study aimed to improve patients' quality of life by managing distressing symptoms. Most patients presented at an advanced stage, necessitating palliative care. Treatment varied based on individual needs and performance status. Of 62 patients, five (8%) died, 20 (32.2%) were lost to follow-up, and 15 (24%) responded to chemotherapy after three cycles. After six cycles, 22 (35.4%) were receiving supportive care.

Malignant obstructive jaundice often presents late, requiring palliative drainage. Percutaneous transhepatic biliary drainage (PTBD) and endoscopic retrograde cholangiopancreatography (ERCP) are common palliative procedures. PTBD is comparable to ERCP in technical success and complications, with reduced mortality and improved survival. PTBD is crucial in cholangitis and sepsis. PTBD indications include cholangitis, pain relief, pruritus, and bilirubin reduction before chemotherapy. PTBD contraindications include uncorrectable bleeding and relative factors like high INR or low platelets. Pre-procedural preparation involves antibiotics, analgesics, and fasting. PTBD technique involves selecting a target duct based on obstruction site and liver parenchyma. PTBD complications include minor issues like pain and major ones like cholangitis, sepsis, and hemorrhage. Biliary stenting, either with plastic or metallic stents, is often performed after PTBD(15).

Various studies in this field are summarised in table 1.

Short-course regimens are frequently favored, spanning 5 to 15 treatment fractions administered over a period of one to three weeks. This condensed timeframe minimizes the burden of treatment on patients, allowing for a balance between symptom relief and convenience. The primary goals of palliative radiotherapy in gallbladder cancer include pain management, often a significant concern for patients.

A study by Yarnold et al.(16) compared single-fraction (8 Gy) radiotherapy to multifraction radiotherapy for painful skeletal metastases. 765 patients with painful skeletal metastases participated in a randomized clinical trial. 12-month survival was 44% in both groups, showing no significant difference. Time to pain improvement, complete pain relief, and pain increase were similar in both groups. Retreatment was more frequent after single-fraction radiotherapy. No significant differences were found in nausea, vomiting, spinal cord compression, or fractures. Single-fraction 8 Gy radiotherapy is as safe and effective as multifraction regimens for at least 12 months.

The specific fractionation schedule and total dose of radiation are carefully determined by the radiation oncologist, considering factors such as the patient's overall health, the extent of the disease, and the specific symptoms being targeted (17,18). It's important to note that individual responses to radiotherapy can vary, and ongoing communication between the patient and the healthcare team is essential to ensure optimal symptom management.

Table 1- Notable studies done in palliative Radiotherapy in Gall bladder cancer.

Author	Study Design	Arm A	Arm B	Results	Conclusion
Khatri et al.(9)	Retrospective	Best supportive care	Palliative Chemotherapy and Radiation	No statistical difference between both Arms Arm B showed better progression free survival in some patients.	ChemoRadiation provides better PFS
Sinha et al.(10)	Randomised controlled	Palliative chemotherapy	Palliative ChemoRadiation	Arm B showed better PFS and OS. LCR was common in ARM A	chemoradiotherapy should be considered a standard treatment option.
Sekar et al.(11)	Randomised controlled	Palliative Chemotherapy	Palliative Radiotherapy	Arm A showed better PFS and ORR	Chemotherapy alone is better than Radiotherapy alone in inoperable LAGBC
Engineer et al.(13)	Prospective	ChemoRadiation followed by surgery	-	Improved ORR with neoadjuvant chemoradiation in Locally advanced GB cancer	Neoadjuvant chemoradiation can facilitate curative resection in LAGBC
Gupta et al.(14)	Prospective	PTBD, Palliative ChemoRadiation, Radiotherapy	-	Symptomatic relief achieved by palliation	Improved quality of life of patients treated with palliative techniques.

CONCLUSION

Palliative radiotherapy helps gallbladder cancer patients manage symptoms like pain, jaundice, nausea, and swallowing difficulties. Radiotherapy targets tumor areas, reducing size and pressure, thus lessening pain, improving biliary drainage, and relieving symptoms. Though not a cure, it improves comfort and well-being by managing pain, improving nutrition, and addressing jaundice, enhancing overall function and quality of life. Emerging techniques of Radiotherapy like IGRT can significantly decrease toxicity

and complications following Radiation. Neoadjuvant ChemoRadiation can be considered standard of care for unresectable locally advanced Gall bladder cancer with intent of curative resection.

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ABBREVIATIONS

1. DFS- Disease free survival
2. OS- Overall Survival
3. ORR- Overall response rate
4. PFS- Progression free survival
5. LCR- Loco-regional Recurrence
6. BSC- Best supportive care
7. LAGBC- Locally advanced Gall bladder cancer