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CLINICAL INVESTIGATION **Gastrointestinal Cancer**

ROLE OF DEFINITIVE RADIATION THERAPY IN CARCINOMA OF UNKNOWN PRIMARY IN THE ABDOMEN AND PELVIS

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Objectives: Carcinoma of unknown primary (CUP) in the abdomen and pelvis is a heterogeneous group of cancers with no standard treatment. Considered by many to be incurable, these patients are often treated with chemotherapy alone. In this study, we determined the effectiveness of radiation therapy in combination with chemotherapy in patients with CUP in the abdomen and pelvis.

Patients and Methods: Medical records were reviewed for 37 patients with CUP treated with radiation therapy for disease located in the soft tissues and/or nodal basins of the abdomen and pelvis at the University of Texas M.D. Anderson Cancer between 2002 and 2009. All patients underwent chemotherapy, either before or concurrent with radiation therapy. Patients were selected for radiation therapy on the basis of histologic type, disease extent, and prior therapy response. Twenty patients underwent definitive radiation therapy (defined as radiation therapy targeting all known disease sites with at least 45 Gy) and 17 patients underwent palliative radiation therapy. Only 6 patients had surgical resection of their disease. Patient and treatment characteristics were extracted and the endpoints of local disease control, progression-free survival (PFS), overall survival (OS), and treatment-related toxicity incidence were analyzed.

Results: The 2-year PFS and OS rates for the entire cohort were 32% and 57%, respectively. However, in patients treated with definitive radiation therapy, the rates were 48% and 76%, and 7 patients lived more than 3 years after treatment with no evidence of disease progression. Nevertheless, radiation-associated toxicity was significant in this cohort, as 40% experienced Grade 2 or higher late toxicities.

Conclusions: The use of definitive radiation therapy should be considered in selected patients with CUP in the soft tissues or nodal basins of the abdomen and pelvis.

Carcinoma of unknown primary, Chemoradiation, Conformal radiation therapy, Intensity-modulated radiation therapy, Lymph node metastasis.

INTRODUCTION

Carcinoma of unknown primary (CUP) is a heterogeneous group of cancers in which regional or distant metastases are detected with no identifiable primary tumor (1). Because CUP represents metastatic disease, the initial treatment in most patients is chemotherapy (1). Unfortunately, in spite of significant improvements in tumor characterization (2, 3), staging (4, 5), and patient selection (6, 7), chemotherapy alone is not curative in most cases (8–12). However, in some patient subsets, the combination of chemotherapy and definitive local therapy can be curative (1, 13). These subsets include patients with metastases to the cervical (14–17) or axillary lymph nodes (18, 19) and isolated metastases to the brain (20). These conditions are characterized by limited overall disease burden and a disease location that is amenable to definitive local therapy.

CUP in the soft tissue and lymph nodes of the abdomen and pelvis is generally considered be incurable. Some investigators have argued that aggressive local therapy is not indicated in these cases because, believing that metastases in these locations indicate widely disseminated disease (21). However, modern imaging (4) and pathologic evaluation (2, 3) techniques have allowed us to more accurately stage and characterize CUP (5). Further, modern conformal radiation therapy techniques have allowed us to deliver definitive radiation therapy to areas of the abdomen and pelvis while sparing surrounding normal tissues (22–27). However, whether definitive local therapy for CUP in the

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abdomen and pelvis is beneficial is unknown. Therefore, the goal of this study was to determine whether radiation therapy was effective in CUP in the modern era, as measured by survival rates, local disease control, and toxicity.

PATIENTS AND METHODS

After approval from our institution's Internal Review Board, patients were identified through a search of the University of Texas M.D. Anderson Cancer Center Department of Radiation Oncology databases. In all, 381 patients with CUP were identified who were treated with radiation between 2002 and 2009. Of these, 40 patients were treated to metastatic sites in the soft tissues or nodal basins of the abdomen and/pelvis. Three of these patients had putative primary disease sites identified during the course of their radiation treatment. As such, the cohort for this analysis comprised a total of 37 patients (Table 1).

Pretreatment evaluation

All patients had undergone a comprehensive physical examination and radiologic evaluation at presentation and had biopsy-proven disease that had been reviewed at M.D. Anderson. Twenty-seven patients (73%) had undergone positron emission tomography–computed tomography scans. Histologic diagnoses were based on morphologic and immunohistochemical findings. When no definitive diagnosis was possible, patients were scored as unclassifiable.

Treatment

All patients received chemotherapy tailored to the histologic diagnosis before or concurrent with radiation therapy. Patients were selected for radiation therapy on the basis of histologic type, disease extent, and prior therapy response. All patients underwent CT-based simulation. Definitive treatment was defined as radiation therapy delivered with the goal of disease eradication targeting all known sites of disease to a dose of at least 45 Gy. The choice to treat patients with definitive therapy was made by the treating radiation physician at the time of consultation. Prophylactic radiation was defined as radiation given to adjacent at risk nodal basins and mucosal surfaces that were not grossly involved with disease.

Follow-up and statistical analysis

Local disease control, progression-free survival (PFS), and overall survival (OS) curves were calculated using the Kaplan-Meier method, and significance tests were based on the log–rank statistic. Correlations between variables were assessed using the Spearman correlation coefficient. Local treatment failure was defined as

Table 1. Patient and treatment characteristics

	Definitive	Palliative	Total
	$n = 20$	$n = 17$	$n = 37$
Sex, *n* (%)			
Male	4 (20%)	6 (35%)	10 (27%)
Female	16 (80%)	11 (65%)	27 (73%)
Median age, years (range)	49 (37–72)	60 (37–74)	55 (37–74)
Histology, *n* (%)			
Adenocarcinoma	6 (30%)	9 (53%)	15 (41%)
Squamous cell carcinoma	10 (50%)	4 (24%)	14 (38%)
Neuroendocrine	0	2 (12%)	2 (5%)
Other	4 (20%)	2 (12%)	6 (16%)
Disease location			
Abdomen	8 (40%)	6 (35%)	14 (38%)
Pelvis	8 (40%)	1 (6%)	9 (24%)
Pelvis + abdomen	3 (15%)	1 (6%)	4 (11%)
Pelvis and/or abdomen + distant	1 (5%)	9 (53%)	10 (17%)
Number of involved sites, *n* (%)			
≤3	13 (65%)	5 (29%)	18 (49%)
>3	7 (35%)	12 (71)	19 (51%)
Chemotherapy, *n* (%)			
Neoadjuvant chemotherapy	11 (65%)	13 (76%)	24 (65%)
Concurrent chemotherapy	16 (80%)	7 (41%)	23 (62%)
Adjuvant or salvage chemotherapy	9 (45%)	11 (65%)	20 (54%)
Response to neoadjuvant chemotherapy, *n* (%)			
Partial/complete response	7 (35%)	4 (24%)	11 (30%)
Stable or progressive disease	4 (20%)	9 (53%)	13 (35%)
Surgical resection			
Preradiation	2 (10%)	0	2 (5%)
Postradiation	5 (25%)	1 (6%)	6 (16%)
Radiation treatment, total dose, Gy (range)	52.5 (50–69.6)	35 (21–40)	50 (21–69.6)
Radiation treatment target, *n* (%)			
Targeting all sites of disease	20 (100%)	5 (29%)	25 (68%)
Prophylactic coverage	15 (75%)	0	15 (41%)
Radiation technique			
Conventional	2 (10%)	11 (65%)	13 (35%)
Three-dimensional conformal radiotherapy	7 (35%)	6 (35%)	13 (35%)
Intensity-modulated radiotherapy	11 (55%)	0	11 (30%)