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Gastrointestinal Cancer

Cancer of Unknown Primary Presenting as Bone-Predominant or Lymph Node-Only Disease: A Clinicopathologic Portrait

Ryan W. Huey,[a] Brandon G. Smaglo,[a] Jeannelyn S. Estrella,[b] Aurelio Matamoros,[c] Michael J. Overman,[a] Gauri R. Varadhachary,[a] Kanwal P.S. Raghav[a]

Departments of [a]Gastrointestinal Medical Oncology, [b]Pathology, and [c]Abdominal Imaging, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Neoplasms • Unknown primary • Immunohistochemistry • Pathology • Antineoplastic agents • Prognosis

Abstract

Background. Cancer of unknown primary (CUP) presenting as bone-predominant (BCUP) or lymph node-only disease (LNCUP) represents two clinically distinct subsets of non-visceral CUP. These present a diagnostic challenge with a large differential of putative primary cancers and defy the "one-treatment-fits-all" approach.

Materials and Methods. We identified patients with BCUP (n = 29) and LNCUP (n = 63) using a prospectively collected CUP database and tumor registry of patients seen at MD Anderson Cancer Center between 2001 to 2017. Clinicopathological characteristics, treatments, and outcomes were abstracted. A control group of non-BCUP/LNCUP cases (n = 443) from the database was used for comparison. Kaplan-Meier method was used to estimate overall survival and compared using log-rank test.

Results. In this cohort, 64% and 60% patients had disseminated disease at diagnosis and 39% and 23% had Culine poor-risk disease in BCUP and LNCUP, respectively. Median overall survival (OS) for BCUP was 14.5 months and for LNCUP was 32.6 months. For BCUP, gemcitabine plus platinum was the most common initial chemotherapy (54%). For LNCUP, carboplatin plus paclitaxel was the most common initial chemotherapy (38%). Radiation was given to 74% of patients with BCUP and 37% of those with LNCUP. On multivariate analysis, poor-risk Culine group (hazard ratio [HR], 1.76; $p < .001$) and high neutrophil-to-lymphocyte ratio (HR, 2.38, $p < .001$) were associated with worse OS.

Conclusion. BCUP and LNCUP are rare subsets within CUP with varying prognosis. Poor-risk Culine group and high neutrophil-to-lymphocyte ratio are associated with poor survival. Select patients with limited metastases can have long-term survival with aggressive multimodality treatment. Careful clinicopathological review can facilitate chances of site-directed therapy. ***The Oncologist*** 2021;26:e650–e657

Implications for Practice: Cancer of unknown primary (CUP) rarely presents as bone-predominant (BCUP) or lymph node-only (LNCUP) disease. This article describes a cohort of each and compares with a larger CUP cohort. Patients with BCUP have unique issues with fractures and pain, often receiving radiation. Overall survival of 14.5 months was similar to a larger CUP comparison cohort. Patients with LNCUP had improved overall survival at 32.6 months, with longer survival in patients without disseminated disease. Culine poor-risk group and neutrophil-to-lymphocyte ratio were associated with worse overall survival. Tips regarding diagnosis and management of these rare malignant subsets are provided.

Introduction

Cancers of unknown primary (CUP) are malignancies diagnosed with metastatic sites for which no primary site can be identified [1]. Management of these cancers present an unique therapeutic challenge. Currently, site-specific therapy or empiric systemic treatment providing adequate coverage for a range of possible primaries is recommended management [2].

The taxonomy of CUP is constantly evolving, with the development of advanced imaging, novel immunohistochemistry,

Correspondence: Kanwal Raghav, M.D., Department of GI Medical Oncology; The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 426, Houston, Texas 77030, USA. Telephone: 713-792-2828; e-mail: kpraghav@mdanderson.org Received October 20, 2020; accepted for publication January 21, 2021; published Online First on February 15, 2021. http://dx.doi.org/10.1002/onco.13700

and molecular profiling. In the era of tailored therapeutic strategies, this presents both an opportunity and a challenge. A focused diagnostic workup to search for the primary cancer site and ascertain the extent of disease is key, so that the patient can proceed to the most appropriate systemic therapy. The majority of patients with CUP present with visceral disease, mainly to liver and lungs. Other, less common, presentations are metastases predominantly to bone (referred to as bone-predominant CUP [BCUP]) or limited to lymph nodes (referred to as lymph node-only [LNCUP]). These uncommon sites for CUP presentation without visceral disease herald a unique subtype within the heterogeneous CUP entity and drive unique approaches in terms of their risk stratification and treatment. As both lymph node and bony metastases can develop far from a primary cancer, the location may not reliably provide an anatomic correlation in the search for the potential primary site and wide differential for putative primary cancers exists [3]. The workup of BCUP additionally poses unique challenges related to limited tissue availability and imaging sensitivity. Management of LNCUP can also be hampered by the diverse histologies, including, but not limited to, squamous cell carcinoma, denocarcinoma, or undifferentiated neoplasms. It is critical to not overlook lymphoma and germ cell cancers, especially when immunohistochemistry does not identify a clear lineage. The extent of disease (limited vs. disseminated) also complicates benefit of or lack-thereof from multimodality therapy. Accurate prediction of survival in CUP is also a challenging issue, and although models like the Culine prognostic model and markers like neutrophil-to-lymphocyte ratio (NLR) exist, their performance for various clinical subsets is largely unknown [4–6].

Given the lack of data and limited understanding of BCUP or LNCUP, we aimed to describe the clinical features and outcomes data of these two unique CUP presentations.

Materials and Methods

We performed a retrospective systematic review of patients with CUP evaluated and treated at The University of Texas, MD Anderson Cancer Center (MDACC) between 2001 and 2017, with emphasis on BCUP and LNCUP. Patients were identified using a prospectively collected CUP database and tumor registry [7]. CUP was defined as a biopsy proven metastatic cancer without a detectable primary site despite a focused diagnostic investigation including clinical, pathologic, and radiographic data. BCUP was defined as CUP presentation with single or multiple metastases to only bone, and LNCUP was defined as presence of lymph node-only disease. Patients with any other visceral site of disease were ineligible. For comparison, we used a historical control group of patients with CUP (between 2012 and 2016) with non-BCUP/LNCUP presentations. Baseline characteristics included age at diagnosis, gender, ECOG performance status, limited site (defined as disease within a single radiation port) versus disseminated metastatic sites at diagnosis, and laboratory parameters. Patients were further risk stratified using the Culine prognostic model for CUP [4]. The study was approved by the institutional review board at MDACC, and a waiver for informed consent was obtained.

Patient data were summarized using descriptive statistics. Overall survival (OS) was determined using date of diagnosis to the date of death and was estimated using the Kaplan-Meier method and 95% confidence intervals (CIs) and compared using log-rank test. Patients alive at last follow-up were censored. Prognostic factors were defined a priori and Cox proportion hazard models were used for multivariate analyses. Results were expressed in hazard ratios (HRs) and with 95% CI.

Results

Patient and Tumor Characteristics

A total of 29 and 63 patients were identified with BCUP and LNCUP, respectively. The baseline characteristics are summarized and compared in Table 1. These were compared with the historical control group of 443 patients with no LNCUP or BCUP. The sum of the patient numbers used in this analysis was thus 535.

For patients with BCUP, median age at diagnosis was 67 years (range, 18–81), and 52% were male. Of these, 18 (64%) presented with disseminated disease at time of diagnosis. Adenocarcinoma and carcinoma (41% each) were the most common histologies. Eleven (39%) cases were poor risk as per Culine prognostic model, and eight (33%) had high NLR. Twenty (74%) of these patients received radiation therapy during their treatment. The most common initial systemic therapy used was a gemcitabine-platinum combination (54%).

Correspondingly, for patients with LNCUP, median age at diagnosis was 61 years (range, 32–89), and 48% were male. Disseminated disease at presentation was seen in 38 (60%) patients. Of the 25 patients with limited disease, 40%, 44%, 8%, and 8% of patients had lymphadenopathy involving the axilla, inguinal or pelvic, cervical, and intra-abdominal regions. The most common histology was carcinoma, seen in 34 (54%) patients, followed by adenocarcinoma in 14 patients (22%). Only four patients were women with axillary-only LNCUP with carcinoma histology, with none having adenocarcinoma. No patients had cervical-only LNCUP with squamous cell carcinoma histology. With respect to the Culine prognostic model, 44 (77%) patients were classified as good risk and 11 (17%) had a high NLR. Approximately 23 (37%) patients received radiation, and the most common initial chemotherapy regimen used was platinum-paclitaxel, used in 16 patients (38%). Comparison with the non-BCUP/LNCUP cohort is shown in supplemental online Table 1. Patients with LNCUP and patients with BCUP differed from patients without BCUP and LNCUP in some key characteristics (Culine risk group, NLR, histology, and receipt of radiation).

Immunohistochemistry and Tumor Testing

We compared the immunophenotypic characteristics of tumors between BCUP and LNCUP patients using the most common immunohistochemistry (IHC) markers based on percentage of positive tests (Fig. 1). Markers were selected for analysis only if they were used in ≥15% cases. In BCUP, carcinomas stained with pankeratin (92%) and cytokeratin 7 (70%) and did not express TTF1 (96%), CDX2 (80%), and cytokeratin 20 (78%). For LNCUP, carcinomas were positive

Table 1. Baseline characteristics

Variable	Patients with BCUP (n = 29), n (%)	Patients with LNCUP (n = 63), n (%)	p Value
Median age, yr	67	61	
Gender			.35
Male	15 (52)	26 (41)	
Female	14 (48)	37 (59)	
Pathology			.26
Adenocarcinoma	12 (41)	14 (22)	
Carcinoma	12 (41)	34 (54)	
Squamous cell carcinoma	1 (3)	8 (13)	
Malignant neoplasm	3 (10)	6 (10)	
Other	1 (3)	1 (2)	
Extent of disease			.72
Limited	10 (36)	25 (40)	
Disseminated	18 (64)	38 (60)	
Culine prognostic model			.11
Good	17 (61)	44 (77)	
Poor	11 (39)	13 (23)	
NLR			.11
Normal	16 (66)	52 (83)	
Elevated	8 (33)	11 (17)	
Receipt of radiation treatment			.001
Yes	20 (74)	23 (37)	
No	7 (26)	40 (63)	
Initial systemic treatment			.02
Carboplatin/paclitaxel	4 (31)	16 (38)	
Gemcitabine/platinum	7 (54)	6 (14)	
Fluoropyrimidine-based	2 (15)	10 (24)	
Other	0	10 (24)	

Note: Percentages reflect cases with data available.
Abbreviation: NLR, neutrophil-to-lymphocyte ratio.

for pankeratin (83%), cytokeratin 7 (82%), and p63 (64%) and were negative for TTF1 (100%), cytokeratin 20 (80%), estrogen receptor (75%), and CDX2 (63%).

In some cases, tumors were able to undergo additional characterization by either next-generation sequencing (NGS) or tissue of origin (ToO) testing. Performance of these tests was limited by the availability of tissue in many cases. Successful NGS and ToO testing was performed for 14% and 10% of tumors, respectively.

Univariate and Multivariate Survival Analysis

Median OS for the BCUP cohort was 14.5 months (95% CI, 10.5–18.5 months) and for the LNCUP cohort was 32.6 months (95% CI, 4.3–60.9 months; Fig. 2). Compared with other CUPs (median OS, 15.6; 95% CI, 13.4–17.9 months), patients with BCUP appeared to have poorer survival (HR, 1.18; 95% CI, 0.7–1.9; p = .43), and patients with LNCUP had a significantly better survival (HR, 0.51; 95% CI, 0.4–0.9; p < .001). On univariate analysis, age $\geq$ 60 years, male sex, disseminated disease, poor-risk Culine group, and high NLR were differentially associated with poorer survival between BCUP and LNCUP (Table 2). On multivariate analysis, LNCUP had significantly better survival compared with other CUP after adjusting for other prognostic factors. Similarly, BCUP showed a trend toward poorer survival (HR, 1.51; 95% CI, 0.9–2.5; p = .11). Additionally, age $\geq$ 60 years (HR, 1.37; 95% CI, 1.1–1.8, p = .014), poor-risk Culine group (HR, 1.76; 95% CI, 1.4–2.3; p < .001), and high NLR (HR, 2.38; 95% CI, 1.8–3.1; p < .001) were independently associated with worse overall survival.

Discussion

In this large cohort of 535 patients with CUP, BCUP and LNCUP represent rare and unique subsets (12% and 5%, respectively). The case illustrations seen in figures 4 and 5 demonstrate key approaches to diagnosis and treatment in patients with BCUP and LNCUP. A summary of our group's practice tips is available in supplemental online Table 2.

Patients with BCUP tend to have a poorer survival as compared with patients with other visceral CUP presentations. Difficulties with tissue acquisition and analysis play a significant role in diagnosis and can delay therapy. Such a delay may play more of a role in survival outcomes for

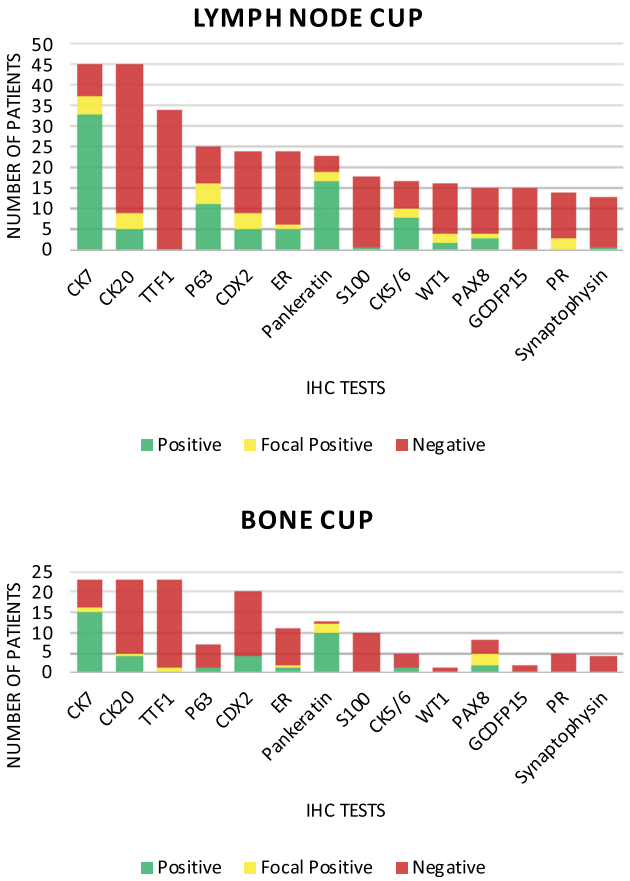


Figure 1. Immunohistochemistry data. Immunohistochemistry data for lymph node-only cancer of unknown primary (LNCUP) and bone-predominant cancer of unknown primary. The IHC markers used in ≥15% of cases of LNCUP are shown.
Abbreviations: CUP, cancer of unknown primary; IHC, immunohistochemistry.

these patients than does a biologic difference. Current routine decalcification protocols for the processing of bone specimens damage nucleic acids, leading to a high failure rate for molecular profiling [8]. Contrary to nonbone tissue with high failure rate in small biopsy or FNA specimens,

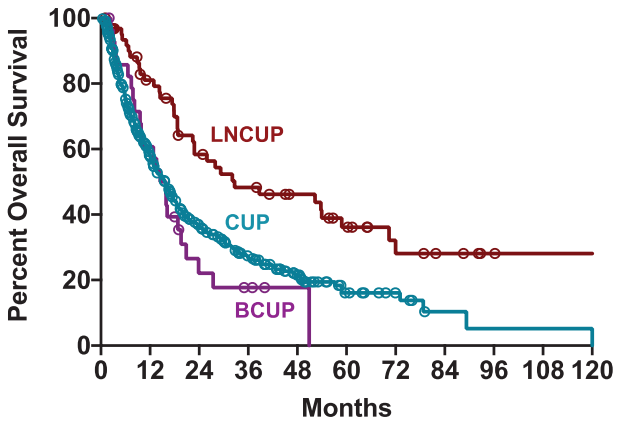


Figure 2. Kaplan-Meier curve of overall survival. Kaplan-Meier survival curves for patients with CUP, bone predominant CUP, and lymph node-only CUP.
Abbreviations: BCUP, bone-predominant CUP; CUP, cancer of unknown primary; LNCUP, lymph node-only CUP.

reports suggest metastatic bone specimens have a higher failure rate even in resection specimens. Surgeons, operating room personnel, and pathologists need guidance and institutional algorithms in place on preservation and processing of resected specimens [8]. There may be a role for multiplex IHC and other emerging technologies in aiding in diagnosis while preserving tissue. The low numbers of successful NGS and ToO testing that were performed in this cohort reflect limitations in tissue availability. As is illustrated in Figure 1, the IHC results for BCUP do not significantly narrow the differential diagnoses. Of the variables that were considered, none was associated with a statistically meaningful impact on survival in BCUP, although disseminated disease, Culine score, and NLR all trended toward such an association. As is illustrated (Fig. 3) by the case example of BCUP, presentation with bone fracture and pain is unique from other types of CUP, as it can necessitate initial treatment in the metastatic setting that is local, rather than systemic [9]. Most patients with BCUP received radiation therapy at some point, further emphasizing the unusually high requirement for local therapy for metastatic palliation in this disease type. Initial need for and proceeding with a local therapy potentially delays the initiation of any systemic therapy for BCUP, which may allow additional, unchecked progression of systemic disease. [10]. Such a delay in systemic therapy for metastatic disease may contribute to the poorer survival of patients with BCUP as compared with patients with visceral CUP. As such, it is important for a multidisciplinary discussion to take place between medical and radiation oncology before proceeding with an initial intervention for BCUP, to ensure the benefits of an initial therapy are balanced with the delay in a subsequent therapy.

In contrast to BCUP, patients with LNCUP had improved survival as compared with those patients with other CUP presentations (Fig. 3). A high NLR seems to be a robust poor prognostic marker as has been previously described in sarcomatoid CUP and other malignancies [5, 6]. Two groups of patients with LNCUP have been classically described as favorable subsets, including isolated squamous cell carcinoma of the cervical lymph nodes, which is generally treated as a head and neck primary cancer, and women with isolated axillary adenocarcinoma, which is often treated as breast cancer in the absence of a diagnostic IHC for another primary cancer [11]. Two important principles for these patients that contribute to their good prognosis are locoregional disease presentation, lending itself to multimodality treatment, and malignancies that are sensitive to chemotherapy and/or radiation [12, 13]. Other subsets have been described in smaller numbers, including squamous cell carcinoma of the inguinal lymph nodes, which may be treated with chemoradiation or surgery, similar to anal cancer [14, 15]. In women, careful examination of the cervix, vagina, and vulva is important to rule out a primary site. Some of these patients may have long-term disease-free survival [15]. Our study found that these patients with limited site LNCUP had a significantly improved overall survival compared with patients with disseminated disease. In addition, these data demonstrate that other groups of patients with limited LNCUP (e.g., isolated

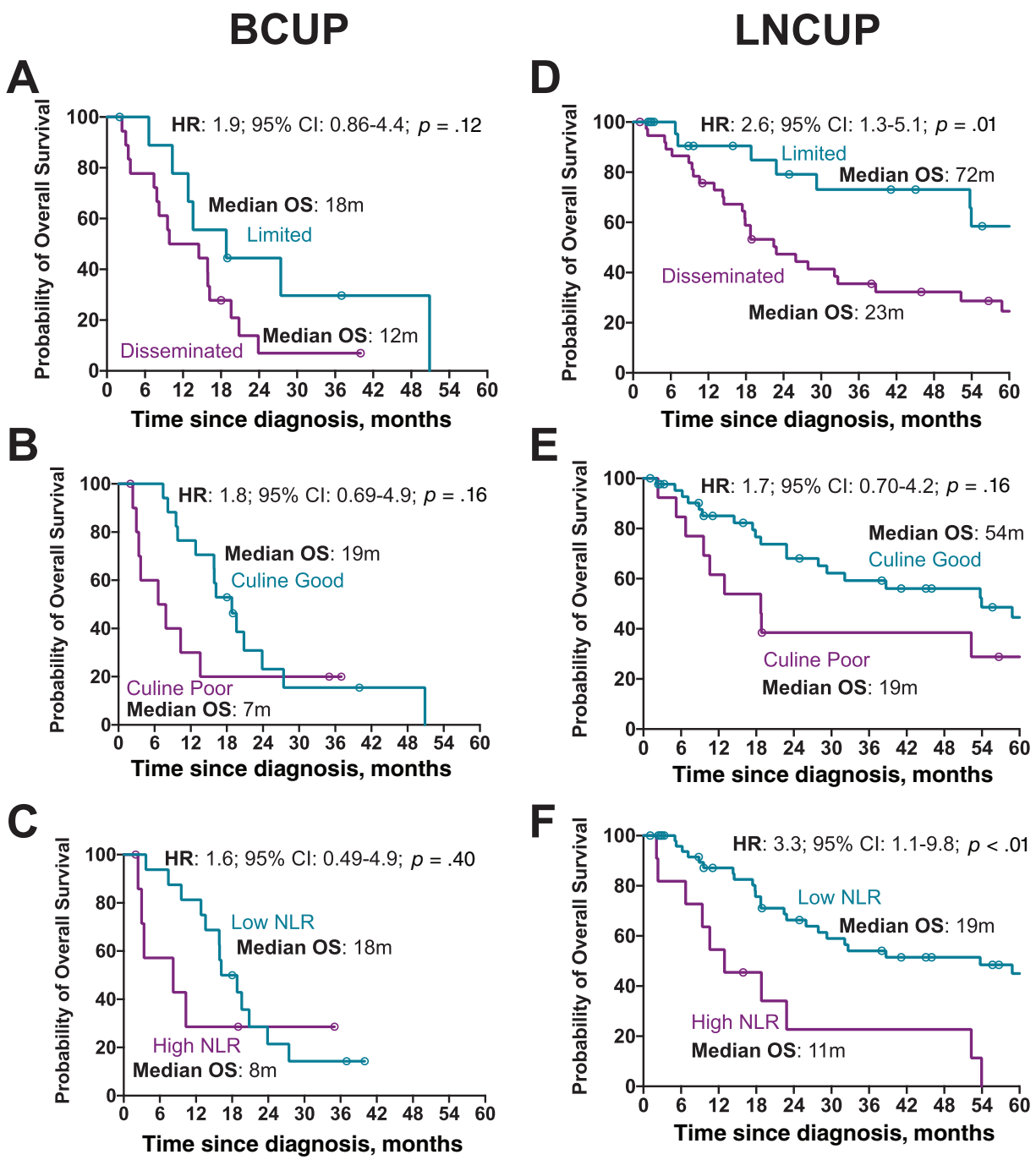


Figure 3. Kaplan-Meier curves of overall survival by patient characteristics. Kaplan-Meier survival curves for patients with bone predominant cancer of unknown primary (CUP) **(A–C)** and lymph node-only CUP **(D–F)**.
Abbreviations: BCUP, bone-predominant cancer of unknown primary; CI, confidence interval; HR, hazard ratio; LNCUP, lymph node-only cancer of unknown primary; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival.

inguinal lymphadenopathy) should perhaps be included as a favorable subset. These patients may be well-suited for aggressive, multimodality therapy, combining systemic therapy with surgery and/or radiation, with the potential for cure. Furthermore, compared with CUP, patients with LNCUP were more likely to have histology of carcinoma or squamous cell carcinoma and less likely to have adenocarcinoma. Immunohistochemistry with a limited panel to include p63 (a squamous cell carcinoma marker) is critical to confirm the diagnosis of carcinoma and exclude other treatable malignancies that are poorly differentiated that may mimic carcinoma (e.g., germ cell tumors and lymphomas). One must have a high index of suspicion to rule out these highly curable malignancies.

In our study, NGS results were limited and did not offer treatment guidance. As such, for these patient cohorts, treatment outcomes were not impacted by profiling results. Very few patient samples were evaluated, mostly in part because of many patients receiving care prior to widespread genomic testing. Limitations in tumor

Table 2. Univariate and multivariate analyses for overall survival

		Univariate analysis			Multivariate analysis	
Factor[a] and category	***n* (%)**	**mOS (95%CI)**	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
CUP site subset						
All CUP[b]	443 (82.8)	15.6 (13.4–17.9)	Reference	<.001		.005
Bone-predominant	29 (5.4)	14.5 (10.5–18.5)	1.18 (0.7–1.9)	.43	1.5 (0.9–2.5)	.11
Lymph node only	63 (11.8)	32.6 (4.3–60.9)	0.51 (0.4–0.7)	<.001	0.59 (0.4–0.9)	.011
Age, yr						
<60	257 (48.0)	18.8 (13.5–24.2)	1.43 (1.2–1.8)	.001	1.37 (1.1–1.8)	.014
≥ 60	278 (52.0)	14.3 (11.4–17.2)				
Sex						
Female	294 (55.0)	19.8 (15.5–24.2)	1.44 (1.2–1.8)	<.001	1.28 (0.9–1.6)	.05
Male	241 (45.0)	15.0 (12.7–17.3)				
Histology						
Adenocarcinoma	293 (54.8)	15.9 (13.4–18.3)	Reference	.007		.06
Carcinoma	169 (31.6)	17.8 (11.6–24.0)	0.77 (0.6–0.9)	.025	0.75 (0.6–1.0)	.05
Others[c]	73 (13.6)	18.8 (0.0–49.0)	0.63 (0.5–0.8)	.006	0.69 (0.5–1.0)	.07
Disseminated						
No	196 (38.3)	19.9 (13.5–26.3)	1.31 (1.0–1.6)	.021	1.14 (0.9–1.5)	.32
Yes	316 (61.7)	15.8 (13.5–18.0)				
Culine prognosis						
Good	242 (50.8)	27.4 (22.2–32.7)	1.98 (1.6–2.5)	<.001	1.76 (1.4–2.3)	<.001
Poor	234 (49.2)	11.0 (8.5–13.4)				
NLR (<5 vs. ≥5)						
Low	336 (70.3)	20.0 (16.6–23.3)	2.46 (1.9–3.3)	<.001	2.38 (1.8–3.1)	<.001
High	142 (29.7)	7.7 (5.8–9.6)				

[a]Some variables have missing values. Percentage has been calculated using known values only.
[b]All CUP includes all other CUP without bone-redominant or lymph node only presentation.
[c]Other histologies include squamous cell carcinoma, malignant neoplasm.
Abbreviations: CI, confidence interval; CUP, cancer of unknown primary; HR, hazard ratio; mOS, median overall survival; NLR, neutrophil-lymphocyte ratio

tissue may present an opportunity for the use of NGS in circulating tumor DNA, which has been shown to be feasible in a CUP population [16]. As additional, actionable mutations are identified for inclusion within the NGS profile platforms, the utility of translating these analyses into actionable therapeutic recommendations should increase, especially in the context of tumor-agnostic therapeutic indications [17].

Chemotherapy is an important treatment modality for both BCUP and LNCUP. The majority of patients received an empiric regimen, with combinations that included either a platinum and taxane, gemcitabine and a platinum, or fluoropyrimidine-based treatment. Patients with BCUP were preferentially treated with gemcitabine-platinum combination, in contrast to LNCUP, in which platinum-paclitaxel was most often used. Options for non-chemotherapeutic systemic treatments may be identified using wide-coverage tumor profiling, which may identify actionable targets fitting into a tumor-agnostic category [18]. Even when identified, obtaining approval for financial coverage for such a medication in these circumstances can be met with resistance. The difficulty in providing precise treatment recommendations, compounded by a typically aggressive behavior of these cancers, make for a poor prognosis in general for CUP [10].

Our study has some limitations beyond sample size. Although our CUP program is involved in the management of most patients with CUP, we believe that LNCUP prevalence is likely underrepresented because of referral bias, as patients with cervical, inguinal, and axillary adenopathy presentations are referred to other services. The time frame of our patient population preceded the wide-scale use of modern NGS techniques. As the various NGS platforms are becoming more commonly applied and consistently complete with regard to inclusion of actionable mutations, such sequencing becomes more applicable to therapeutic selection. In addition, with the approvals of immunotherapy and several targeted therapies in recent years, these patients (if treated today) may have been eligible for novel cancer therapies that could have potentially improved survival. Although not readily available retrospectively, having an understanding of these tumors' mutational burden or mismatch repair deficiencies may elucidate a greater understanding of immunotherapy treatment options for these difficult-to-treat tumors. Finally, although we have looked at key factors influencing outcomes, the sample size limits

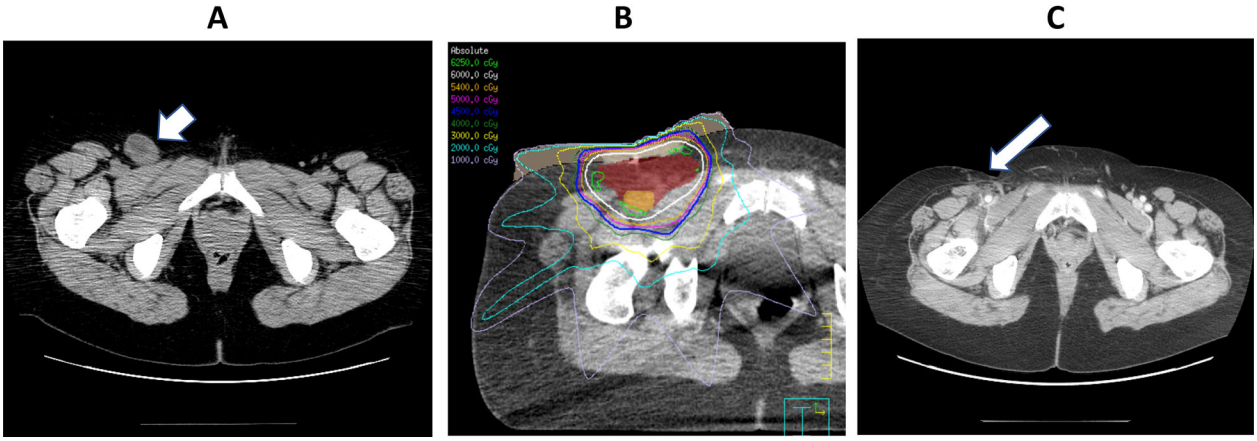
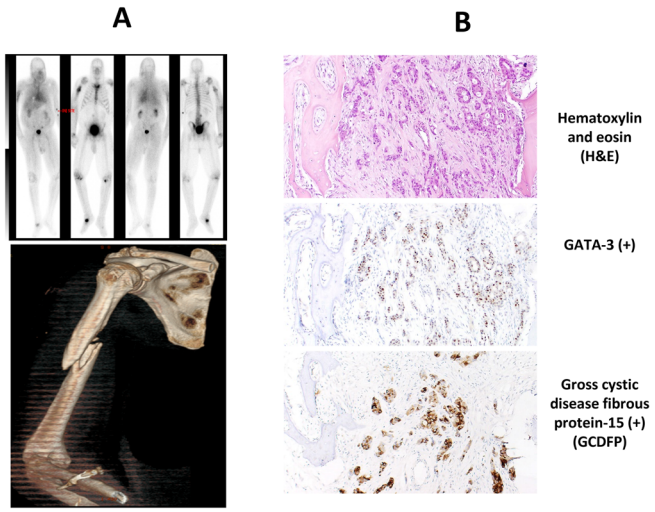


Figure 4. Approach to solitary inguinal squamous cell carcinoma. A 48-year-old woman developed swelling in her right inguinal region. When this failed to improve with antibiotics, she underwent a computed tomography (CT) scan of the abdomen and pelvis, which showed a solitary 3 cm right inguinal mass **(A; short white arrow)**. Excisional lymph node biopsy showed a poorly differentiated squamous cell carcinoma with positive margins. Previous pap smears were negative. Rectal exam with anoscopy, sigmoidoscopy, and repeat gynecology examination including high-risk human papillomavirus assay were negative. CT scan of the chest, abdomen, and pelvis did not reveal a primary tumor. Multidisciplinary consensus from radiation and surgical teams was to proceed with radiation over surgery (combination not recommended given risk of lymphedema). She received anus-sparing, pelvic radiation, 60 Gy in 25 fractions to the right inguinal and external iliac regions **(B)** with concurrent weekly cisplatin (20 mg/m^2) and capecitabine, Monday to Friday (850 mg/m^2 b.i.d.). Follow-up CT scan 2 months after completion of therapy and serial positron emission tomography–CT scans showed no evidence of disease **(C; long white arrow)**, and the patient has remained in remission for 8 years.



C

Pathology marker	Profile in male putative breast cancer
ER	97-99%
PR	82-90%
Her-2 (FISH)	8-10%
GCDFP-15	75%
GATA-3	98%

Figure 5. Bone predominant CUP presentation. A 78-year-old man suffered a right humerus pathologic fracture, which was treated surgically at an outside hospital with an intramedullary nail. Initial pathology revealed metastatic carcinoma with immunohistochemistry (IHC) positive for CK7 and pankeratin and negative for CK20 and p63. Differential diagnosis for the putative primary included lung, biliary, breast, and renal cancers **(A)**. He underwent postoperative radiation and was seen at The University of Texas, MD Anderson Cancer Center 5 months after his initial diagnosis. Bone scan revealed diffuse bony metastases. Computed tomography (CT) imaging revealed one area of suspicious liver metastasis and prominent hilar nodes. Given the concern for another fracture, he underwent left hemiarthroplasty with curettage and cementation of the left humeral lesion followed by postoperative radiation (30 Gy). Pathology was consistent with adenocarcinoma, and IHC matched the prior lesion, albeit negative for lung and prostate markers. Patient was treated with broad spectrum carboplatin + paclitaxel for progressive liver metastases followed by pemetrexed. Tissue of origin analysis was most consistent with a breast primary. Mammogram and breast ultrasound were unrevealing. Additional IHC analysis reported GCDFP-15 (+), GATA-3 (+), 10% estrogen receptor (+), <1% progesterone receptor (+), and 2+ for HER2, and HER2 FISH was negative **(B)**. Patient received capecitabine, gemcitabine, tamoxifen, and doxorubicin in sequence until declining functional status. The patient succumbed to progressive metastatic disease, 23 months after his initial diagnosis. This case illustrates the broad differential of bone-predominant presentation and the role of IHC and ToO assays in select patients to guide decision-making. **(C)** Common IHC for male profile breast cancer.[19,20]
Abbreviations: ER, estrogen receptor; FISH, fluorescence in situ hybridization; PR, progesterone receptor.

comparisons for some variables that may also mitigate these outcomes. These limitations should be considerations for future prospective studies.

Conclusion

BCUP and LNCUP are distinct entities with unique clinicopathologic characteristics within CUP heterogeneous presentations. Patients with BCUP have poorer prognosis than patients in the all-CUP category, and patients with LNCUP have a better prognosis than those in the all-CUP category. Focused evaluation and communication with the pathologist remain key in challenging cases, not only on presentation but throughout the cancer treatment journey. With the availability of novel targeted therapies and the improved availability of NGS, we expect the utility of NGS for this patient population to grow and help guide future therapy beyond platinum doublet cytotoxic therapies and to further expand with the refinement of liquid NGS. Dedicated clinical trials with appropriate stratification for these subsets within the large heterogeneity in CUP can help improve outcomes in this challenging orphan disease.

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Author Contributions

Conception/design: Ryan W. Huey, Brandon G. Smaglo, Gauri R. Varadhachary, Kanwal P.S. Raghav
Provision of study material or patients: Gauri R. Varadhachary, Kanwal P.S. Raghav
Collection and/or assembly of data: Ryan W. Huey, Brandon G. Smaglo
Data analysis and interpretation: Ryan W. Huey, Brandon G. Smaglo, Kanwal P.S. Raghav
Manuscript writing: Ryan W. Huey, Brandon G. Smaglo, Gauri R. Varadhachary, Kanwal P.S. Raghav
Final approval of manuscript: Ryan W. Huey, Brandon G. Smaglo, Jeannelyn S. Estrella, Aurelio Matamoros, Michael J. Overman, Gauri R. Varadhachary, Kanwal P.S. Raghav

Disclosures

The authors indicated no financial relationships.

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