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**The Role of Site-Specific Therapy for Cancers of Unknown of Primary:  
A Meta-Analysis**

**Short title:** Site-Specific Therapy for Cancers of Unknown of Primary

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19    **Highlights**

20    This paper is a meta-analysis of the trials evaluating site-specific treatments in CUP.

21    No significant survival benefit with site-specific versus empiric chemotherapy.

22    There was significant heterogeneity across the prospective studies.

23    Current evidence is insufficient to recommend site-specific therapy in CUP.

24    However, certain patients with CUP may still benefit from tailored treatments.

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## **Abstract**

Cancers of unknown primary (CUP) are among the most common causes of death due to cancer, are associated with a poor prognosis, and have few therapeutic options available. Molecularly-guided site specific treatments were explored based on the assumption that CUP are similar in their response to treatment to predicted primary tumors. Given the discordant results between these studies, a meta-analysis using a random-effects model and the inverse variance method was performed. MEDLINE and conference abstracts of American Society of Clinical Oncology (ASCO) and European Society of Medical Oncology (ESMO) meetings were searched from inception until November 2019. A trend towards improved OS was found with site-specific versus empiric treatment for CUP (HR = 0.73; 95% CI 0.52-1.02). There was significant heterogeneity across the 4 studies ( $I^2 = 79\%$ ;  $p = 0.002$ ) but no significant difference between the treatment effect in the two subgroups (randomized vs. non-randomized;  $p = 0.07$ ). The test for overall effect for PFS, which had only been reported for the two randomized studies, was not statistically significant (HR = 0.93; 95% CI 0.74-1.17), with little heterogeneity between studies ( $I^2 = 0\%$ ;  $p = 0.77$ ). The results of this meta-analysis highlight the significant heterogeneity between the prospective studies comparing molecularly tailored to empiric therapy for CUP and the need for other randomized studies including only primary tumors with available effective therapies.

## **Keywords**

Cancer of unknown primary; Tailored therapy; Site-specific; Empiric

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## Current Perspectives

Cancers of unknown primary (CUP) are a heterogeneous group of metastatic tumors, for which a primary site origin cannot be identified despite a standardized diagnostic work-up<sup>1</sup>. It accounts for 1-2% of all malignancies and ranks as the seventh cause of mortality in patients with cancer<sup>2</sup>. Largely, two subsets of patients can be identified based on clinicopathologic criteria<sup>3</sup>. The first encloses a minority of patients (15-20%) that is chemosensitive and has an overall favorable prognosis<sup>3</sup>. The second subset includes the larger category of patients (80-85%) that cannot be assigned to a primary tumor and commonly present a dismal prognosis with empiric CUP chemotherapy regimens<sup>4</sup>. The efficacy of site-specific treatments in the favorable subsets of patients with CUP makes compelling evidence to assess tailored therapy in patients within the unfavorable subsets<sup>5</sup>. Moreover, case reports and series had suggested that the use of tailored therapies in the unfavorable subset leads to favorable clinical outcomes<sup>6,7</sup>.

Two prospective studies have reported on the outcomes of site-specific therapy in patients with CUP. The largest is a subset of 194 patients that had both sufficient tumor material for the assay and received assay-directed therapy. This subset was compared to a retrospective cohort from the same consortium that had been treated by empiric chemotherapy, and were found to have significantly improved overall survival (OS; hazard ratio of 0.63 [95% CI 0.60-0.66]; hazard ratio unpublished - obtained from authors)<sup>8</sup>. In another study of 216 patients with CUP, 188 (87%) had had their primary tumors identified using a microarray-based DNA methylation signatures<sup>9</sup>. Patients treated with tailored therapy (n = 31) achieved an OS benefit in comparison to those treated with empiric CUP regimens (n = 61) with a hazard ratio (HR) of 0.31 (95% CI 0.14-0.70)<sup>9</sup>.

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79 The efficacy of site-specific therapy was further addressed in two randomized controlled  
80 trials enrolling patients with CUP into tailored therapy or empiric CUP regimen arms. The  
81 first is a phase II study comparing molecularly-driven site-specific therapy and the  
82 combination of paclitaxel plus carboplatin <sup>10</sup>. The two treatment arms showed similar OS (HR  
83 = 1.03; 95% CI 0.68-1.56) and progression free survival (PFS; HR = 0.88; 95% CI 0.59-1.33) <sup>10</sup>.  
84 The second study is a phase III trial that randomized 243 patients into tailored therapy or the  
85 combination of cisplatin plus gemcitabine <sup>11</sup>. No statistically significant differences in PFS (HR  
86 = 0.95; 95% CI 0.72-1.25) or OS (HR = 0.92; 95% CI 0.69-1.23) were found between the two  
87 treatments arms <sup>11</sup>. Given these discordant results, we performed a meta-analysis of these  
88 studies while taking into account the inherent heterogeneity of the included studies.

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90 MEDLINE and conference abstracts of American Society of Clinical Oncology (ASCO) and  
91 European Society of Medical Oncology (ESMO) meetings were searched from inception until  
92 November 2019 for studies evaluating molecularly tailored therapies for CUP. All prospective  
93 studies comparing molecularly tailored to empiric therapies for CUP were included. All data  
94 were abstracted by two authors independently (ER and ZB). The meta-analysis was  
95 performed using a random-effects model and the inverse variance method in order to  
96 account for possible heterogeneity in treatment effect due to differences in the molecular  
97 tests used, study design, and the included patient populations in the four studies. A  
98 subgroup analysis by study design (randomized vs. non-randomized) was performed in order  
99 to better account for this factor. The primary comparison was that of tailored versus empiric  
100 therapies for CUP. The primary endpoint was OS and the secondary endpoint was PFS. All  
101 analyses were done using the Review Manager software, version 5.3 (The Nordic Cochrane

Center, The Cochrane Collaboration, Copenhagen, Denmark). The threshold for statistical significance for the tests of overall effect and subgroup comparison was 0.05 and that for the tests of heterogeneity was 0.10. The  $I^2$  coefficient was used to quantify the degree of heterogeneity within and between subgroups. All hypothesis tests were formulated prior to data collection.

The pooled analysis included 628 patients treated empirically and 398 treated by tailored therapies. For the primary outcome, a non-statistically significant trend towards improved OS was found with tailored versus empiric treatment for CUP (Figure 1; HR = 0.73; 95% CI 0.52-1.02). Within the non-randomized subgroup (N= 225 tailored and 457 empiric), the effect was statistically significant (HR = 0.56; 95% CI 0.26-0.96) but there was significant heterogeneity between the two included studies ( $I^2$ = 65%;  $p$ =0.09). Within the randomized controlled trials subgroup (N= 173 tailored and 171 empiric), the effect was not statistically significant (HR = 0.95; 95% CI 0.75-1.21). There was also significant heterogeneity across the 4 studies ( $I^2$ = 79%;  $p$ =0.002) but no significant difference between the treatment effect in the two subgroups (randomized vs. non-randomized;  $p$ =0.07). The test for overall effect for PFS, which had only been reported for the two randomized studies, was not statistically significant (HR = 0.93; 95% CI 0.74-1.17), with little heterogeneity between studies ( $I^2$ = 0%;  $p$ =0.77).

The results of this meta-analysis highlight the significant heterogeneity between the prospective studies comparing molecularly tailored to empiric therapy for CUP. The possible sources of heterogeneity between studies include the study design (randomized vs. non-randomized), the type of molecular testing performed to identify the primary site of origin

(methylation vs. RNA-based), the types of systemic therapies included in the tailored and empiric therapy arms, and the breakdown of expected primary sites (and how sensitive to tailored and empiric therapies they are expected to be) <sup>8-11</sup>. While no overall statistically significant effect in favor of tailored therapies was found in this study, certain selected subgroups of patients may still benefit from this approach. The study by Moran et al. had the lowest point estimate of the HR among all the included studies <sup>9</sup>. One of the main differences between this study and the other included studies was that the assay used to infer the primary tumor type was DNA methylation-based (as opposed to the others which were all RNA-based) <sup>9</sup>. Another potential difference between this study and the three other studies was the breakdown of the predicted primary tumors, whereby the most frequent predicted primary was breast carcinoma in the study by Moran et al. as opposed to pancreaticobiliary carcinoma which is generally associated with a poor prognosis in each of the three other studies <sup>8-11</sup>. Moreover, certain patient subgroups did not receive the therapies that constituted the standard of care at the time of enrollment of these studies such as immune checkpoint inhibitors and novel targeted therapies for kidney cancer, melanoma, and non-small cell lung cancer. Yet, the GEFCAPI04 trial showed that the subgroup of predicted primary tumors that are known to be unresponsive to empiric CUP regimens (such as kidney cancer, melanoma, and colorectal carcinoma) had a trend towards improved OS with tailored therapies (2-year estimate of 24.3% vs. 10.4% and HR= 0.74; 95% CI 0.36-1.51), although the study had been underpowered to detect such an effect <sup>11</sup>. Finally, the population of CUP patients enrolled into clinical trials and diagnosed in clinical practice has changed substantially in recent years due to improved immunohistochemistry-based diagnostics. This has restricted the definition of CUP to more select cancer types, for which specific protein markers are not readily available (such as squamous cell and pancreato-



biliary tumors) and limits the applicability of the data generated from the earlier periods of enrollment of all the included trials.

This meta-analysis highlights the difficulty of evaluating the role of tailored therapies in patients with CUP. While the overall effect of tailored compared to empiric therapies was negative, subgroup analyses of the primary studies and the results of this analysis suggest that selected patients may benefit from such an approach, site-specific therapy for all comers cannot be recommended at this time. The differences in design of the studies and the small sample sizes limit the conclusions of the present analysis. Future randomized controlled trials that use standardized diagnostic tests and the contemporaneous standard of care for patients with identified primaries, particularly in the more responsive cancer types, are highly needed to accurately address the question of tailored therapies for CUP.

## Conflicts of interest

ER, ZB, NP: None declared

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210   filed on ERCC2 mutations and chemotherapy response, chromatin mutations and  
211   immunotherapy response, and methods for clinical interpretation.  
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215

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## 218   **References**

219   **1.** Fizazi K, Greco FA, Pavlidis N, et al: Cancers of unknown primary site: ESMO Clinical  
220   Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol Off J Eur Soc Med  
221   Oncol 26 Suppl 5:v133-138, 2015

222   **2.** Rassy E, Pavlidis N: The currently declining incidence of cancer of unknown primary.  
223   Cancer Epidemiol 61:139–141, 2019

224   **3.** Pavlidis N, Pentheroudakis G: Cancer of unknown primary site. Lancet Lond Engl  
225   379:1428–1435, 2012

226   **4.** Pavlidis N: Forty years experience of treating cancer of unknown primary. Acta Oncol  
227   46:592–601, 2007

228   **5.** Daud AI: Removing the Unknown From the Carcinoma of Unknown Primary. J Clin Oncol  
229   31:174–175, 2012

230 **6.** Rassy EE, Pavlidis N: The current evidence for a biomarker-based approach in cancer of  
 231 unknown primary [Internet]. *Cancer Treat Rev* 0, 2018[cited 2018 May 8] Available from:  
 232 [https://www.cancertreatmentreviews.com/article/S0305-7372\(18\)30055-0/fulltext](https://www.cancertreatmentreviews.com/article/S0305-7372(18)30055-0/fulltext)

233 **7.** Gross-Goupil M, Massard C, Lesimple T, et al: Identifying the primary site using gene  
 234 expression profiling in patients with carcinoma of an unknown primary (CUP): a feasibility  
 235 study from the GEFCAPI. *Onkologie* 35:54–55, 2012

236 **8.** Hainsworth JD, Rubin MS, Spigel DR, et al: Molecular gene expression profiling to predict  
 237 the tissue of origin and direct site-specific therapy in patients with carcinoma of unknown  
 238 primary site: a prospective trial of the Sarah Cannon research institute. *J Clin Oncol Off J Am*  
 239 *Soc Clin Oncol* 31:217–223, 2013

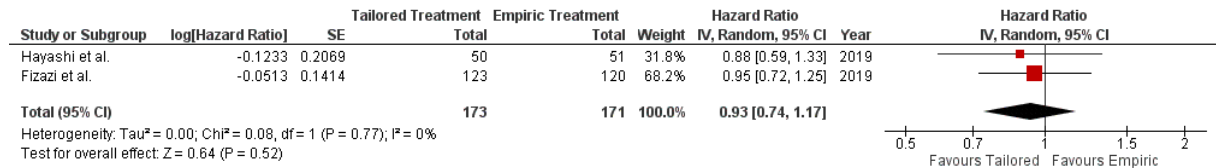
240 **9.** Moran S, Martínez-Cardús A, Sayols S, et al: Epigenetic profiling to classify cancer of  
 241 unknown primary: a multicentre, retrospective analysis. *Lancet Oncol* 17:1386–1395, 2016

242 **10.** Hayashi H, Kurata T, Takiguchi Y, et al: Randomized Phase II Trial Comparing Site-Specific  
 243 Treatment Based on Gene Expression Profiling With Carboplatin and Paclitaxel for Patients  
 244 With Cancer of Unknown Primary Site. *J Clin Oncol Off J Am Soc Clin Oncol* 37:570–579, 2019

245 **11.** Fizazi K, Maillard A, Penel N, et al: LBA15\_PRA phase III trial of empiric chemotherapy  
 246 with cisplatin and gemcitabine or systemic treatment tailored by molecular gene expression  
 247 analysis in patients with carcinomas of an unknown primary (CUP) site (GEFCAPI 04)  
 248 [Internet]. *Ann Oncol* 30, 2019[cited 2019 Oct 18] Available from:  
 249 [https://academic.oup.com/annonc/article/30/Supplement\\_5/mdz394/5578411](https://academic.oup.com/annonc/article/30/Supplement_5/mdz394/5578411)

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**Figure 1A:** Hazard ratio for PFS (95% CI) in CUP trials comparing tailored and empiric chemotherapy regimens



**Figure 1B:** Hazard ratio for OS (95% CI) in CUP trials comparing tailored and empiric chemotherapy regimens

