Original Article

Clinical and pathologic features correlated with rare favorable survival in patients with *BRAF*^{V600E} mutated colorectal cancer

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Background: *BRAF*^{V600E} mutations occur in fewer than 10% of all patients with metastatic colorectal cancer (CRC) and arise from sessile serrated adenomas. Despite efficacy with targeted therapies against MAPK signaling and with immunotherapies in this population, survival outcomes for patients with *BRAF*^{V600E} mutated metastatic CRC in general are poor. Characteristics distinguishing patients with *BRAF*^{V600E} mutated metastatic CRC with favorable versus unfavorable outcomes have not been well annotated.

Methods: Records of 187 patients with *BRAF*^{V600E} mutated metastatic CRC evaluated at MD Anderson Cancer Center between 2005–2020 were reviewed. Patients with the shortest and longest metastatic survival (N=25 for each group) were compared. Associations between prognostic group and clinical/pathologic features were measured by odds ratio and for median survival by log-rank testing.

Results: Median metastatic survival differed between the 2 *BRAF*^{V600E} mutated metastatic CRC populations (8.6 *vs.* 83.9 months, hazard ratio 32; P<0.0001). Patients with poor survival more commonly had hepatic involvement [75% *vs.* 28%, odds ratio (OR) 8.1, 95% confidence interval (CI): 2.3–29; P=0.001]. Patients with favorable survival were more likely to develop metachronous metastases (52% *vs.* 16%, OR 5.7, 95% CI: 1.5–21; P=0.01) and undergo definitive locoregional therapy to metastatic disease (40% *vs.* 0%, OR 34.5, 95% CI: 1.9–630; P=0.01). Microsatellite instability (36% *vs.* 4%, OR 19.8, 95% CI: 2.2–180; P=0.008) and prior tobacco exposure (44% *vs.* 16%, OR 4.1, 95% CI: 1.1–15.6, P=0.04) were associated with a favorable prognosis. Durable responses to MAPK-targeted therapies and immunotherapy were noted in the favorable group.

Conclusions: A small fraction of patients with *BRAF*^{V600E} mutated metastatic CRC can achieve excellent long-term survival which belies conventional context and is driven by either surgical metastectomy or by systemic treatment options. While poor overall prognosis remains the recognized outcome for most patients with *BRAF*^{V600E} mutated metastatic CRC, it is possible that few may achieve exceptionally favorable survival.

Keywords: *BRAF*; colorectal cancer (CRC); metastasis; immunotherapy; metastectomy

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Introduction

BRAF^{V600E} mutations, present in approximately 8–10% of all patients with metastatic colorectal cancer (CRC) (1,2), typically develop along the sessile serrated adenoma pathway (3) and activate oncogenic MAPK signaling which drives tumor cell proliferation and distant spread (4). These genomic aberrations are often accompanied by microsatellite instability, right-sided primary colorectal tumors, hypermethylation, peritoneal metastases, female gender, and advanced age (5-7). Prognostically, patients with *BRAF*^{V600E} mutated metastatic CRC fare poorly relative to their *BRAF*$^{wild\text{-}type}$ counterparts, with shortened overall survival and rapid clinical deterioration (8-10). Disease control with standard cytotoxic regimens utilized for metastatic CRC are short and overall unsuccessful (11), highlighting the need for new therapeutic interventions.

In recent years, immune checkpoint blockade agents targeting PD-1 with or without CTLA-4 have resulted in prolonged survival for patients with microsatellite instability-high (MSI-H) metastatic CRC (12-14), present in approximately 30–40% of *BRAF*^{V600E} mutated CRC (15,16). Combinations of targeted therapies against BRAF and EGFR have led to improvements over standard options for this population (17). Most notably here, doublet therapy with encorafenib plus cetuximab demonstrated for the first time prolonged overall survival relative to irinotecan/cetuximab by over 3 months in the recently reported phase III BEACON study (18). Here, objective responses to therapy with encorafenib and cetuximab were observed in 20% of patients, although acquired resistance, resulting in eventual failure of treatment benefit, develops in the majority of patients who initially respond to these therapies (19,20).

Despite these initially promising findings, patients with *BRAF*^{V600E} mutated metastatic CRC in general continue to be regarded as unlikely to experience favorable, sustained survival upon detection of distant metastatic disease. To characterize further clinical and pathologic features associated with exceptionally favorable and unfavorable outcomes, we performed a retrospective review of patients with *BRAF*^{V600E} mutated metastatic CRC as defined according to the shortest and longest survival durations. We present the following article in accordance with the REMARK reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-21-471/rc).

Methods

Under a research protocol approved by the Institutional Review Board, electronic databases were reviewed retrospectively to identify patients with adenocarcinoma of the colon or rectum harboring a *BRAF*^{V600E} mutation with distant metastatic disease who were evaluated at the University of Texas – MD Anderson Cancer Center between 2005 and 2020. Testing for mutation and microsatellite status was performed in a Clinical Laboratory Improvement Amendments (CLIA)-approved environment. Relevant demographic, clinical, pathologic, and survival data—including age, gender, tobacco use, primary tumor sidedness, onset of metastasis, metastatic organ involvement, microsatellite status, and treatment history—were collected when available for each patient. Next-generation sequencing for testing of concomitant mutations in genes such as *APC*, *TP53*, *PIK3CA*, and *SMAD4*, all relevant to colorectal cancer.

Overall survival was defined as the time from the date of initial detection of distant metastatic disease to the date of last contact or to the date of death, depending on the vital status for each patient. Patients with *BRAF*^{V600E} mutated metastatic CRC were then ranked in ascending order of metastatic survival, and those 25 patients with overall survival of 50 months or greater were selected as the basis for the "longest survival" (LS) group. Accordingly, patients (N=25 for each group) with the longest and shortest overall survivals were incorporated to form the "longest survival" and "shortest survival" (SS) cohorts, respectively. In order to avoid confounding by patients who had been recently diagnosed with *BRAF*^{V600E} mutated metastatic CRC and started on systemic treatment for whom the clinical outcome/phenotype was too early to ascertain, patients in the SS group must have been deceased for inclusion. Patients in this SS group were selected for a cohort size to match that of the LS group, who alternatively were included regardless of vital status.

Statistical analysis

Descriptive statistics were utilized to annotate population features (IBM SPSS Statistics 24; Chicago, Illinois). Associations between clinical/pathologic characteristics and survival classification were estimated at odds ratios (OR) and tested for significance using a Fisher's exact test.

Recurrence-free survival (RFS) for patients undergoing definitive locoregional therapies to distant metastases was calculated as the date of resection (metastectomy patients) or date of radiotherapy initiation until the date of clinical recurrence or until the date of death, whichever came first. Median RFS and OS were calculated according to the Kaplan-Meier method (GraphPad Prism 8 Software; La Jolla, California). Differences between median survival, with accompanying hazard ratio (HR), were compared between groups using a log-rank test, with a two-sided P value less than 0.05 considered significant.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional review board at MD Anderson (No. LAB09-0373) and individual consent for this retrospective analysis was waived.

Results

Available records from 187 patients evaluated at MD Anderson Cancer Center with *BRAF*^{V600E} mutated metastatic CRC diagnosed between October 2005–April 2020 were reviewed. Median follow-up time for the entire population was 21 months (range, 1.8–110 months). The 25 patients with the shortest OS and the longest OS represent the worst and best (13% of the studied population, respectively). There was a sizable difference in median OS between the two groups [8.6 versus 84 months; HR 32, 95% confidence interval (CI): 13–74; Figure S1]. Notably, in the LS group, all patients lived longer than 48 months following their initial diagnosis of *BRAF*^{V600E} mutated metastatic CRC. Thirteen patients in this favorable group were still alive at the time of data analysis, 11 of whom were not receiving any antineoplastic therapy in the absence of radiographically detectable and/or clinically active disease.

Demographic information comparing the two *BRAF*^{V600E} mutated CRC populations are listed in *Table 1*. Patients in the LS group trended towards an older age at the time of diagnosis of metastatic disease (60.2 years versus 55.7 years, P=0.08). Patients in the LS group were more likely to have a history of tobacco exposure (44% *vs.* 16%, OR 4.1, 95% CI: 1.1–15.6, P=0.04). Sidedness of the primary tumor across the colon and rectum was relatively evenly distributed, with right-sided tumors present in 68% and 84% of the LS and SS cohorts, respectively. All 25 patients within the LS group had had their primary tumors resected during their clinical course, whereas 11 of the 25 patients in the SS group had primary tumors which were not surgically resected. Consistent with this association between unresectable primary tumors and the SS group (OR =40.4, 95% CI: 2.2–700; P=0.01), patients in the SS group were more likely to present with synchronous metastases (84% versus 48%; OR =5.7, 95% CI: 1.5–21; P=0.01). Here, 13 of the 25 (52%) patients within the LS group developed distant metastatic disease after completion of initial treatment for localized CRC.

As seen in *Table 2*, tumors from patients in the LS group were more likely to be MSI-H (36% versus 4%; OR =19.8, 95% CI: 2.2–180; P=0.008) and have a mucinous histology (44% versus 12%; OR =5.8, 95% CI: 1.4–24; P=0.02). Poorly differentiated histology was reported in 48% of the LS and 76% of the SS groups. Patients in the SS group were more likely to have multiple distant organs with metastatic disease (OR =5.1, 95% CI: 5–18, P=0.01), with 44% of these patients having 3 or more unique organs involved. Over half of the patients in the LS group harbored only one organ site with metastatic involvement. Across both cohorts, the peritoneum (27/50, 54%) and liver (26/50, 52%) were the most common sites of metastatic disease. However, as seen in *Figure 1*, only the liver was differentially involved when comparing the two populations, more common in the SS group (76% versus 28%, OR 8.1, 95% CI: 2.3–29; P=0.001). Involvement of other distant sites like the lung, peritoneum, lymph nodes, and bone were otherwise relatively uniform between the two groups. There were no significant differences in frequencies of co-occurring mutations (SS *vs.* LS groups) for *APC* (10% *vs.* 37%, P=0.15), *TP53* (80% *vs.* 58%, P=0.24), *PIK3CA* (19% *vs.* 18%, P=0.96), and *SMAD4* (20% *vs.* 32%, P=0.51).

The median number or total lines of systemic therapy received in each group was 2 (*Table 3*). Notably, 10 patients in each cohort received only one line of systemic treatment for metastatic disease. 7 (28%) of these patients received 4 or greater lines of systemic treatment, relative to 0 in the worst survival group. 8 patients (32%) in each group received combination targeted therapies including BRAF on clinical trials. 4 patients (3 with MSI-H tumors and one with microsatellite stable (MSS) tumor) in the LS group received immunotherapy agents targeting PD-1 +/- CLTA-4. Given the known benefit of immunotherapy for patients with MSI-H, *BRAF*^{V600E} mutated metastatic CRC, we conducted a sensitivity analysis, in which we excluded these four patients from the LS group, and found that the trends

Table 1 Patients' clinical characteristics

Characteristics	Longest survival (LS)	Shortest survival (SS)	P value
Age (years, median)	60.2	55.7	0.08
Gender, n [%]			0.77
Male	11 [44]	10 [40]	
Female	14 [56]	15 [60]	
Tobacco use, n [%]	11 [44]	4 [16]	0.04
Primary tumor site, n [%]			0.19
Right colon	17 [68]	21 [84]	
Left colon	8 [32]	4 [16]	
Primary tumor intact, n [%]			0.01
Yes	0	11 [44]	
No	25 [100]	14 [56]	
Timing of initial metastases, n [%]			0.01
Synchronous	12 [48]	21 [84]	
Metachronous	13 [52]	4 [16]	
Number of metastatic organs involved, n [%]			0.02
1	14 [56]	5 [20]	
2	7 [28]	9 [36]	
3	4 [16]	11 [44]	
Liver involvement, n [%]			0.001
Yes	7 [28]	19 [76]	
No	18 [72]	6 [24]	
Peritoneum involvement, n [%]			0.61
Yes	15 [60]	12 [48]	
No	10 [40]	13 [52]	
Lung involvement, n [%]			0.07
Yes	4 [16]	10 [40]	
No	21 [84]	15 [60]	

in clinical and pathologic associations distinguishing the LS and SS groups remained unaltered.

Records were reviewed to identify the intervention most associated with prolonged overall survival with the 23 patients in the LS group with adequate clinical data available (*Table 4*). Patients in this cohort were more likely to undergo a definitive locoregional therapy (e.g., surgery or definitive radiotherapy) to sites of distant metastatic involvement relative to the SS cohort (40% versus 0%; OR =34.5, 95% CI: 1.9–630; P=0.02). All 8 patients who underwent metastectomy had received neoadjuvant chemotherapy. In every case, preoperative imaging confirmed interval improvement following systemic treatment. The median duration of neoadjuvant chemotherapy prior to surgery was 5 months (range, 3–22). This was the most common contributor to prolonged OS relative to various systemic

Table 2 Pathologic characteristics

Characteristics	Longest survival (LS)	Shortest survival (SS)	P value
Microsatellite status, n [%]			0.008
Microsatellite stable	10 [40]	22 [96]	
Microsatellite instability-high	9 [36]	1 [4]	
Status unknown	6 [24]	2 [8]	
Differentiation, n [%]			0.06
Well or moderately	12 [48]	6 [24]	
Poorly	12 [48]	19 [76]	
Unknown	1 [4]	–	
Mucinous tumor, n [%]			0.02
Present	11 [44]	3 [12]	
Absent	14 [56]	22 [88]	
Signet ring histology, n [%]			0.19
Present	1 [4]	4 [16]	
Absent	24 [96]	21 [84]	

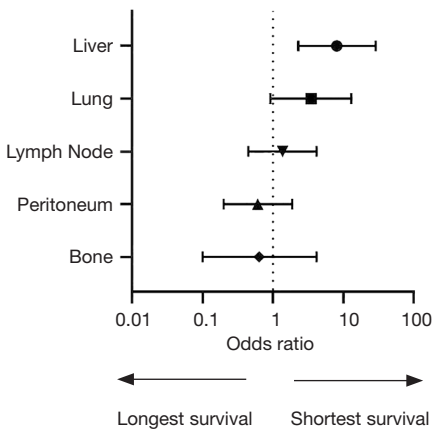

Figure 1 Association between organ site of metastatic involvement and LS and SS groups. LS, longest survival; SS, shortest survival.

therapies. Indeed, the 5 patients who remain without disease recurrence after locoregional intervention have the 5 longest times for follow-up (53, 64, 67, 69, and 80 months) off any additional therapy among all patients with *BRAF*^{V600E} mutated metastatic CRC analyzed. Median PFS of these patients following completion of locoregional therapy was 58.1 months (*Figure 2*). For the 4 patients with survival benefitting by MAPK-directed agents, median PFS was 14.0 months, with a range of 10.1–74.9 months. The 2 patients here who remain on these therapies were both started over 5 years prior to the time of data analysis. Prolonged survival benefit was driven by immunotherapy in 4 patients, with all 3 of the MSI-H metastatic CRC patients experiencing no evidence of recurrent, progressive disease after a median of 48 months from initial treatment start.

Discussion

Our results here show that a small fraction of patients with *BRAF*^{V600E} mutated metastatic CRC can achieve prolonged survival, despite poor prognostic implications associated with this subpopulation. In our study, the 25 patients with *BRAF*^{V600E} mutated metastatic CRC who fared the best, accounting for approximately 15% of the entire group analyzed, all had survival which exceeded 48 months following their first detection of metastatic disease. The majority of the patients in this small group still remain alive and do not require continued antineoplastic treatment. This heterogeneity in clinical outcomes is possibly reflective of an underlying biologic diversity represented within the *BRAF*^{V600E} mutated metastatic CRC population.

Survival outcomes in the prognostically favorable group were driven by a variety of multidisciplinary interventions. The majority of patients here with survival long enough to be followed for years were diagnosed and treated for

Table 3 Treatment of metastatic disease

	Longest survival (LS)	Shortest survival (SS)	P-value
Lines of systemic therapy			0.04
1	10	10	
2	7	11	
3	1	4	
4 or greater	7	0	
Locoregional therapy to distant disease			0.02
Yes	10	0	
No	15	25	

Table 4 Intervention linked to prolonged metastatic survival

	N	PFS range (months)
Locoregional therapy	10	20.3–80.6
Metastectomy	8	
Radiotherapy	2	
BRAF-directed targeted therapy	4	10.1–74.9
Immunotherapy	4	15.9–49.7
Microsatellite instability-high	3	
Microsatellite stable	1	
Systemic chemotherapy	2	94.7–115.2

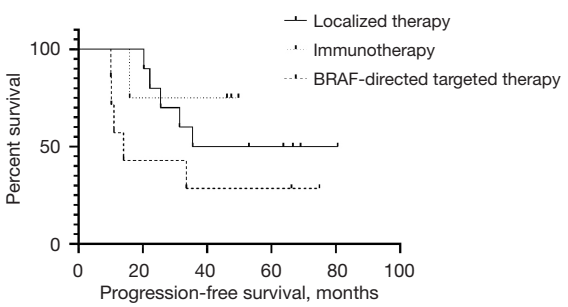

Figure 2 Survival among patients in the LS group according to associated intervention. LS, longest survival.

their *BRAF*^{V600E} mutated metastatic CRC long before either immunotherapy or targeted therapies like encorafenib and cetuximab became FDA-approved treatment options for these patients. Approximately 40% of patients with *BRAF*^{V600E} mutated metastatic CRC concomitantly feature microsatellite instability (10), a predictive biomarker for benefit to immunotherapy in patients with solid tumors including CRC (12). Therefore, it is likely that, with maturing data in the years to come, prolonged OS will be further expanded into this subset of patients, as initial studies with anti-PD-1 antibodies with or without anti-CTLA-4 antibodies have demonstrated sustained anti-tumor activity in these MSI-H patients for tumors that are *BRAF*^{V600E} and *BRAF*$^{wild\text{-}type}$ alike (13,14).

Targeted therapies against oncoproteins critical to MAPK signaling like BRAF, EGFR, and MEK have resulted recently in improvements in survival outcomes and offer new therapeutic opportunities for patients with *BRAF*^{V600E} mutated metastatic CRC (17,18,21). Response rates with these combinations range from 15–30% (18,19,21-23). Nonetheless, acquired resistance develops and leads to loss of disease control for the majority of patients treated with these agents. In our study here, three patients remained on various MAPK-directed therapies as part of investigational protocols for over 2 years. Here, 2 of these 3 patients experiencing exceptional disease control have continued to receive study treatment for more than 60 months.

RNA-based characterizations have separated two distinct transcriptomic phenotypes—BRAF mutation 1 (BM1), characterized by upregulation of KRAS/Akt signaling, and BM2, characterized by disruption of cell cycle homeostasis (24). Post-hoc analyses of tumor profiling from patients with *BRAF*^{V600E} mutated metastatic CRC treated with dabrafenib, trametinib, and panitumumab have demonstrated improved responses and survival outcomes for the BM1 subgroup and have provided initial signal for transcriptomic associations for predicting responses to MAPK-directed therapies in this context (25). In our study,

archival tissue was unavailable for classification of BM status for our patients with prolonged treatment benefit. However, it is possible that future studies may validate the relevance of BM class as a predictive biomarker and thereby enrich patients with *BRAF*^{V600E} mutated metastatic CRC who may exceptionally benefit from these agents, especially if the tumors are MSS and less likely to respond to immunotherapy as monotherapy.

To our surprise, many patients within the prognostically favorable LS group achieved excellent long-term survival despite a *BRAF*^{V600E} mutated status due to treatment of oligometastases with metastectomy or with definitive radiotherapy. For this group, median RFS approaches 60 months, with the majority of this small, selected cohort of patients presumably cured and off any ongoing treatment. Complete resections of distant metastatic disease for patients with CRC have been associated with favorable long-term outcomes in carefully selected cases (26). Retrospective series of patients with metastatic CRC undergoing hepatectomy have linked *BRAF*^{V600E} mutations with worse RFS and more unfavorable mortality after surgery (27,28). While these patients in general have a poor overall prognosis with an aggressive underlying tumor biology, our findings suggest that it is still possible, albeit uncommonly, for a selected patients with *BRAF*^{V600E} mutated metastatic CRC to benefit from curative-intent surgeries. One series from the Mayo clinic reported outcomes from 52 patients with liver-limited *BRAF*^{V600E} mutated metastatic colorectal cancer and reported a median OS after metastectomy exceeding 25 months (29), providing further support for the use of surgical resection in a specific subgroup. However, given the generalized higher likelihood for poor survival in the context of *BRAF*^{V600E} mutation, patients here should be considered most carefully in a multidisciplinary fashion in the context of *BRAF*^{V600E} mutation status to select for those most likely to derive extended survival benefit.

We recognize that not all patients may have been genotyped for *BRAF*^{V600E} mutations given that we included patients as far back as 2005 in this analysis of a large subset of patients with CRC. While a small number of cases limited us from more definitively characterizing the features of these patients with prolonged survival who underwent definitive locoregional therapies, we did seek to identify clinical and/or pathologic characteristics different in the best- versus worst-survival patients with *BRAF*^{V600E} mutated metastatic CRC. Microsatellite instability was more prevalent in the favorable prognostic group, although the majority of patients in this cohort who were tested still had MSS tumors. Across all stages of CRC, microsatellite instability has been annotated as a prognostically favorable feature (30-33), likely driven by increased neoantigen load and heightened immune recognition (34).

Patients in the LS group expectedly had lower overall distant tumor burden with fewer number of distant organ sites involved with cancer. While involvement to the peritoneum has been associated with *BRAF*^{V600E} mutations (6) and was the most common site for metastasis in our cohort, spread to the liver was more common in the worst-survival group, present in 76% of cases. On the other hand, patients in the LS group were more likely to develop metachronous metastases. The poor-survival patients more commonly presented with synchronous metastases, further supporting the likelihood of symptomatology reflective of an underlying higher tumor burden at the time of initial diagnosis (and not endoscopic detection during routine cancer screening evaluations).

A history of tobacco use was associated with an increased likelihood of improved survival among patients with *BRAF*^{V600E} mutations. While exposure to cigarette smoking has been associated with the development of CRC that is characterized by *BRAF*^{V600E} mutations and the CpG Island Methylator Phenotype (CIMP) (10,35), to our knowledge this is the first report to correlate survival within this molecular annotation according to tobacco use. Hypermethylation in CIMP-high CRC has been linked to the development of sporadic, non-Lynch Syndrome microsatellite instability. Validation of this finding in additional cohorts could serve to identify tobacco-related pathogenic drivers which alter the underlying tumor phenotype of specific *BRAF*^{V600E} mutated colorectal cancers that in turn lead to improved survival outcomes.

We recognize certain limitations in generalizing the findings of our retrospective review to the entire population of patients with *BRAF*^{V600E} mutated metastatic colorectal cancer. First, that most patients were diagnosed and managed for their distant metastases prior to the knowledge and availability of immunotherapy and or therapies targeting BRAF and EGFR likely reflect an underestimation of survival outcomes amid the current landscape of therapeutic options in this context. Second, the inclusion of patients who were able to travel to a high-volume, tertiary academic referral center reflects an existing ascertainment bias which excludes a sizable fraction of patients with highly advanced

disease burden at initial presentation who are unable to withstand treatments long enough to seek second opinions. Nonetheless, median OS of the SS group (8.6 months) is less than that of other population-based series estimating survival more expansively. Therefore, our population is likely reflective of a truly unfavorable prognostic subset for patients with *BRAF*^{V600E} mutated metastatic CRC.

In this series, surgical resection represented a curative modality for selected patients in our analysis, with recurrence-free survival exceeding 4 years in multiple cases. These patients should be selected carefully by a multidisciplinary team, but we believe that in thoroughly considered patients with *BRAF*^{V600E} mutated metastatic CRC, improved (even curative) survival can be offered by metastatectomy. Consistent with recent advances demonstrating improved patients' lifespan with newer agents, immunotherapy and targeted therapy combinations against BRAF and EGFR appeared to extend selectively overall survival in certain patients with *BRAF*^{V600E} mutated metastatic CRC. In summary, it is important for clinicians to remain open-minded that a selected small subset of patients with *BRAF*^{V600E} mutated metastatic CRC may achieve durable survival, despite this molecular feature traditionally considered a harbinger for an especially grim outcome for most patients with this subclass of colorectal cancer.

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Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-21-471/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-21-471/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-21-471/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional review board at MD Anderson (No. LAB09-0373) and individual consent for this retrospective analysis was waived.

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Supplementary

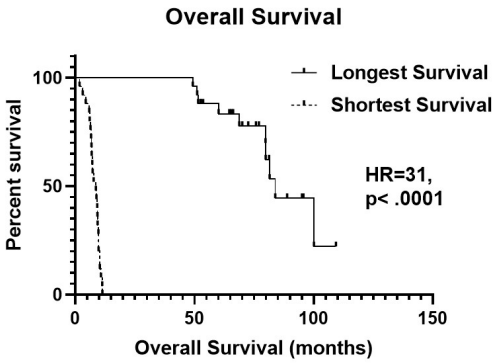

Figure S1 Overall survival for the LS and SS groups.

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