A Comparison of Treatments and Outcomes for Medullary versus Nonmedullary Colon Cancer: A Single Institutional Experience Showing a Worse Prognosis for Stage 3 Disease

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Received 11 June 2019; Revised 6 January 2020; Accepted 17 February 2020; Published 28 March 2020

1.Introduction

Medullary colon cancer (MCC) was differentiated from nonmedullary colon cancer (NMC) as a subtype of adenocarcinoma by the World Health Organization (WHO) and is described as poorly differentiated or undifferentiated tumors with solid sheets of cells lacking glandular formation [1]. This variant is commonly mismatch repair deficient with microsatellite instability and is also characterized by prominent eosinophilic cytoplasm, a pushing type border, marked lymphocytic infiltration, small nuclei, and prominent nucleoli [2].

While data regarding histologic differences between MCC versus NMC are prominent, literature regarding differences in treatment and survival for MCC compared to NMC with poor or undifferentiated pathology appear to be limited and conflicting. Prognosis for MCC is thought to be better compared to NMC since it rarely presents with nodal metastases or metastatic disease [2, 3]. Prior studies showed MCC patients have a better prognosis than undifferentiated (UD) NMC [3–5]. However, one study showed UD MCC typically present at stage 3 may actually have a worse prognosis than NMC of the same stage [3]. Since these tumors more commonly occur in elderly, it is possible that the inconsistent survival outcomes may be secondary to increased surgical morbidity or limited adjuvant treatments.

We aimed to retrospectively examine treatment and survival differences between MCC and NMC within the
Kras mutations. Patients with MCC were also more likely to be right sided with 72.7% of the MCC patients vs. 41.9% of NMC patients (p > 0.032). Tumor location was more likely to be significantly different between MCC vs. NMC (25.0% vs. 72.4%, p = 0.004). Only 4 patients underwent chemotherapy with stage 3 MCC. Reasons for not receiving adjuvant chemotherapy in this group were patient refusal, comorbidities, or death. There was only 1 patient with MCC stage 4 disease, and therefore no conclusion could be drawn about differences in these patients.

When comparing the overall survival for all resected MCC vs. NMC by pathologic stage, only stage 3 patients were found to be significantly different (15.3 vs. 61.9 months, p < 0.0001). When comparing stage 3 MCC vs. PD/UD NMC, survival again was decreased for MCC (15.3 vs. 47.2 months, p = 0.001) (Table 3). The Kaplan–Meier curve is displayed in Figure 1. Resected stage 3 PD and UD patients were then further separated and compared. Median overall survival continued to be worse for MCC vs. NMC for both groups. Overall survival was 25.7 months (n = 6) for PD MCC and 15.3 months for UD MCC (n = 9) vs. 39.6 months for PD NMC (n = 67), and 53 months for UD NMC (n = 40) (p = 0.003) (Figure 2). While 7 patients (22.6%) with MCC vs. 149 patients (10.4%) with NMC underwent contiguous organ resections, survival comparisons showed MCC continued to have a worse survival even without contiguous organ involvement (19.6 months vs. 78.2 months, p < 0.0001). To determine if the worsened survival was secondary to difference in receipt of adjuvant chemotherapy, the resected stage 3 patients were compared. Median survival was not significantly different (p = 0.06).

4. Discussion

Previous studies on MCC reported similar demographics to our findings, showing that MCC patients are older, predominantly female, and with right-sided tumors [3–5, 7]. However, our patient demographics do differ as compared to prior literature. Using the SEER database, Thirunavukarasu et al. identified 50 cases of MCC that more commonly presented as stage 2 disease as well as a higher rate of PD versus UD histology [3]. Wick et al. compared 68 patients with MCC with 35 PD “enteric” colorectal carcinomas and to have stage 2 (36.4%) or stage 3 (48.8%) disease (p = 0.004).

A comparison of treatments received for MCC vs. NMC and MCC vs. PD/UD NMC can be seen in Table 2. Thirty-one patients (93.9%) with MCC and 1433 (87.0%) NMC underwent surgical resection. Seven patients (22.6%) with MCC vs. 149 (10.4%) NMC underwent resection of contiguous organs. No MCC patient received radiation, and 6 (18.2%) patients received chemotherapy only in the adjuvant setting. The 2 patients who did not undergo surgery did not have clinical staging available and did not undergo any treatments. When comparing all MCC to NMC PD/UD for all included patients, MCC were less likely to receive adjuvant chemotherapy (18.2% vs. 45.2%, p = 0.008).

For each pathologic stage (stages 1–3), other treatments received for surgically resected MCC vs. NMC were then compared. No significant differences in treatments (radiation or chemotherapy) were seen for stages 1 and 2 MCC vs. NMC. Of all Stage 3 patients undergoing surgical resection, MCC were less likely to receive chemotherapy compared to NMC (25.0% vs. 72.4%, p = 0.004). Only 4 patients underwent chemotherapy with stage 3 MCC. Reasons for not receiving adjuvant chemotherapy in this group were patient refusal, comorbidities, or death. There was only 1 patient with MCC stage 4 disease, and therefore no conclusion could be drawn about differences in these patients.
15 neuroendocrine carcinomas and found MCC less commonly presents as stage 3 or 4 disease [7]. Our patient population was different, where the most common stage was stage 3 (48.5 % stage 3 vs. 36.4% stage 2) and UD pathology was also more common (36.4% PD vs. 60.6% UD).

Multiple prior studies also showed overall survival was favorable for MCC vs. NMS. Pyo et al. in 2016 found the overall survival rate of MCC higher than PD or UD NMC [5]. Wick et al. found that the MCC patients had a favorable prognosis with a 5-year mortality of 40% compared to 59% for the PD carcinomas [7]. Lastly, Thirunavukarasu et al. found that OS was improved compared to NMC, except for stage 3 patients with UD pathology [3]. In our series, all stage 3 MCC patients, despite differentiation, were found to have a worse prognosis than PD and UD NMC with a difference in over 46 months.

While Knox et al. compared MCC to other colorectal cancers with mismatch repair deficiencies and still found MCC to have a better prognosis, they also found patients with MCC may have a higher mortality at 30 days after

### Table 1: Patient characteristics for MCC vs. NMC and PD/UD NMC.

|                | MCC Total (n = 33) | NMC Total (n = 1775) | MCC vs. NMC PD/UD (n = 292) | MCC vs. PD/UD NMC | p valuea | p valueb |
|----------------|-------------------|----------------------|-----------------------------|-------------------|---------|---------|
| Age            | 79.3 ± 10.2       | 68.3 ± 13.3          | 70.2 ± 13.2                 | <0.0001           | 0.002   |
| Sex            |                   |                      |                             |                   |         |         |
| Female         | 26 (78.8%)        | 869 (49%)            | 169 (57.9%)                 | 0.001             | 0.020   |
| Male           | 7 (21.2%)         | 906 (51%)            | 123 (42.1%)                 |                   |         |         |
| Charlson/Deyo score |            |                      |                             |                   |         |         |
| 0              | 19 (57.6%)        | 1,342 (75.6%)        | 212 (72.6%)                 | 0.013             | 0.032   |
| 1              | 9 (27.3%)         | 309 (17.4%)          | 62 (21.2%)                  | 0.001             | 0.054   |
| ≥2             | 5 (15.2%)         | 124 (7%)             | 18 (6.2%)                   |                   |         |         |
| Location primary site |            |                      |                             |                   |         |         |
| Ascending colon/cecum | 24 (72.7%)     | 744 (41.9%)          | 160 (54.8%)                 | 0.004             | 0.032   |
| Not ascending colon/cecum | 9 (27.3%)    | 984 (55.4%)          | 130 (44.5%)                 |                   |         |         |
| Unknown/other  | 0                 | 47 (2.7%)            | 2 (0.7%)                    |                   |         |         |
| Path stage     |                   |                      |                             |                   |         |         |
| 1              | 2 (6.1%)          | 287 (16.2%)          | 12 (4.1%)                   | 0.004             | 0.032   |
| 2              | 12 (36.4%)        | 386 (21.8%)          | 57 (19.5%)                  |                   |         |         |
| 3              | 16 (48.8%)        | 391 (22%)            | 107 (36.6%)                 |                   |         |         |
| 4              | 1 (3%)            | 258 (14.5%)          | 62 (21.2%)                  |                   |         |         |
| Unknown/other  | 2 (6.1%)          | 453 (25.5%)          | 54 (18.5%)                  |                   |         |         |
| Grade          |                   |                      |                             | <0.0001           | 0.001   |
| Well differentiated | 0              | 121 (6.8%)           | 0                           |                   |         |         |
| Moderately differ | 0              | 1,113 (62.7%)        | 0                           |                   |         |         |
| Poorly differentiated | 12 (36.4%)  | 198 (11.2%)          | 198 (67.8%)                 |                   |         |         |
| Undiffer/anaplastic | 20 (60.6%)  | 94 (5.3%)            | 94 (32.2%)                  |                   |         |         |
| Unknown/other  | 1 (3%)            | 249 (14%)            | 0                           |                   |         |         |

MCC, medullary colon cancer; NMC, nonmedullary colon cancer; PD, poorly differentiated; UD, undifferentiated.

### Table 2: Treatments for MCC vs. NMC and MCC vs. PD/UD NMC.

|                | MCC Total (n = 33) | NMC Total (n = 1775) | MCC vs. NMC PD/UD (n = 292) | MCC vs. PD/UD NMC | p valuea | p valueb |
|----------------|-------------------|----------------------|-----------------------------|-------------------|---------|---------|
| Surgery        |                   |                      |                             |                   |         |         |
| No surgery     | 2 (6.1%)          | 227 (12.8%)          | 32 (11%)                    | 0.424             | 0.553   |
| Surgery        | 31 (93.9%)        | 1544 (87%)           | 260 (89%)                   |                   |         |         |
| Unknown        | 0                 | 4 (0.2%)             | 0                           |                   |         |         |
| Radiation      |                   |                      |                             |                   |         |         |
| No             | 33 (100%)         | 1,749 (98.5%)        | 287 (98.3%)                 | 0.484             | 0.449   |
| Yes            | 0                 | 26 (1.5%)            | 5 (1.7%)                    |                   |         |         |
| Chemotherapy   |                   |                      |                             |                   |         |         |
| None           | 27 (81.8%)        | 1,200 (67.6%)        | 157 (53.8%)                 | 0.529             | 0.008   |
| Neoadjuvant    | 0                 | 13 (0.7%)            | 3 (1%)                      |                   |         |         |
| Adjuvant       | 6 (18.2%)         | 547 (30.8%)          | 132 (45.2%)                 |                   |         |         |
| Neoadjuvant + adjuvant | 0      | 12 (0.7%)            | 0                           |                   |         |         |
| Intraop with other therapies | 0 | 3 (0.2%)             | 0                           |                   |         |         |

MCC, medullary colon cancer; NMC, nonmedullary colon cancer; PD, poorly differentiated; UD, undifferentiated.
resection [4]. After reviewing our institution’s outcomes, our worse prognosis may be secondary to increased comorbidities, increased rate of UD pathology, and increased stage 3 tumors, thus making surgery less tolerated with increased postoperative mortality and higher risk of recurrence. MCC were less likely to get chemotherapy where only 4 of the 15 patients with stage 3 MCC who underwent surgery received chemotherapy. While the number of patients receiving chemotherapy is small and thus comparisons between these groups difficult, those that did not receive chemotherapy had a median overall survival of less than 1 month, highlighting a similar increased postoperative mortality. Resection of other contiguous organs did not lead to increased comorbidities.

In conclusion, our data showed that stage 3 MCC, with both PD and UD histology overall had a worse prognosis than NMC, contradicting some prior published literature. Our series indicate that surgery in this population may have increased risks for postoperative complications and death secondary to other comorbidities and a higher tumor stage with increased UD histology, increasing the risk of recurrence. Limitations of this study include a small sample size, retrospective nature, and a limited geographic population base. Because MCC is a relatively new diagnosis, there is ample room for studies in the future to elucidate the true prognosis of subtypes of MCC with a wider population base.

### Data Availability

The data used to support the findings of this study are included within the article.

### Conflicts of Interest

The authors declares that there are no conflicts of interest regarding the publication of this paper.
Acknowledgments

The research and publication of this article were funded by the Geisinger Health System.

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