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Molecular Tumor Subtypes of Colorectal Cancer and Their Association with Patient Survival

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In this dissertation, the association between molecular tumor subtypes of colorectal cancer and patient prognosis was investigated. The aims were to summarize the currently proposed molecular subtype classifications of colorectal cancer, to evaluate the external applicability of the identified classifications in an independent patient population, to investigate patient survival by combinations of microsatellite status and BRAF (V-raf murine sarcoma proto-oncogene, serine/threonine kinase) mutations, and to explore patient response to adjuvant chemotherapy by microsatellite status and stage.

In a systematic review of the literature, four databases were searched using terms related to colorectal cancer, molecular markers, molecular classifications, and patient prognosis. Six studies that included three or more molecular markers and provided an estimation of survival for each subgroup met the inclusion criteria and were included in the review. A variety of methodologies to define molecular classifications of colorectal cancer were used in the included studies. Three studies suggested subtype classifications based on microsatellite instability and methylation status and on BRAF or KRAS (Kirsten rat sarcoma proto-oncogene, GTPase) mutations. A qualitative synthesis of results showed that subtypes including microsatellite stable tumors and mutations in BRAF or KRAS had worse survival than those with no such mutations and that not all subtypes including tumors with microsatellite instability were associated with better survival.

An external validation analysis was performed using data from the population-based DACHS (Darmkrebs: Chancen der Verhütung durch Screening) study by constructing tumor subtypes equal to those of the three classifications identified in the systematic review. Survival analyses were conducted adjusting for the same set of confounders and restricting the population to match the one included in the original studies. One study found that subtypes with BRAF or KRAS mutations had worse cancer-specific survival, however the results were not statistically significant. This result was confirmed in the external validation analysis performed on the DACHS population, where the estimates were similar. A second study found that subtypes including tumors with microsatellite instability had better cancer-specific survival; however,

this was not the result in the external validation analysis, because differences in the stage distribution among patients with microsatellite instability hindered comparability of results. A third study, based on a clinical trial cohort, found worse survival for BRAF and KRAS mutated microsatellite stable cancers and no significant associations for tumors with microsatellite instability. These results were confirmed in the validation analysis. In analyses among additional patient subgroups that were not investigated in the original studies, the results of the validation analysis did not differ, extending the validity of some of the subtypes to more patient subgroups.

Furthermore, the association of different combinations of microsatellite instability status and BRAF mutations with patient survival was investigated. Cox proportional hazard regression models were used to determine cancer-specific, relapse-free and overall survival. Results were included in a meta-analysis to compare and combine the findings with those of similar studies. Tumors with microsatellite instability were more commonly found in early stage (I-II) patients and showed a non-significant tendency towards better survival, regardless of the BRAF mutation status. Microsatellite stable cancers with BRAF mutations were more commonly found in advanced stages (III-IV), and had worse survival compared to those with no BRAF mutations. This finding was only significant among patients with advanced stage of disease. The meta-analysis included results from nine publications and corroborated the findings for microsatellite stable, BRAF mutated cancers and additionally showed statistically better survival for tumors with microsatellite instability and no BRAF mutations.

Finally, the association between adjuvant chemotherapy and survival by stage of disease and microsatellite status of the tumor was explored in resected stage II and III colon cancer patients. Balance between treated and untreated patients with regard to potential confounders was achieved by including propensity score weights in Cox regression models. A meta-analysis of results specific for stage II patients with microsatellite instability was conducted to compare the results with previously reported literature. Patients who received adjuvant chemotherapy had better survival compared to those treated with surgery alone, independent of stage or microsatellite status of the tumor. Few cancer-related deaths were observed among stage II patients, none of which occurred in patients with microsatellite instable tumors who received chemotherapy.

In conclusion, not all hitherto proposed molecular subtype classifications of colorectal cancer predict survival for all patient subgroups, and none of them were integrated into the existing staging system. Microsatellite instability is a recognized marker indicating good prognosis; however, this association is highly dependent on stage of disease and on the presence of other

genetic mutations. Microsatellite stable tumors with BRAF mutations have a worse prognosis compared to those with no BRAF mutations, and the results presented here provide further insights into how this association is stage-specific. Adjuvant chemotherapy seemed to be beneficial, not only for stage III patients, but also for stage II patients with microsatellite instability, for whom chemotherapy is currently not recommended. The results presented in this dissertation extend and provide further evidence of the importance of colorectal cancer molecular subtypes in the rapidly evolving field of personalized medicine.