Cancer Immunology Miniatures

Cancer Immunology Research

Tumor MHC Class I Expression Improves the Prognostic Value of T-cell Density in Resected Colorectal Liver Metastases

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Abstract

Tumor-infiltrating lymphocytes (TIL) in colorectal cancer liver metastases (CLM) have been associated with more favorable patient outcomes, but whether MHC class I (MHC-I) expression on cancer cells affects prognosis is uncertain. Immunohistochemistry was performed on a tissue microarray of 158 patients with CLM, who underwent partial hepatectomy with curative intent. Using the antibody HC-10, which detects HLA-B and HLA-C antigens and a minority of HLA-A antigens, MHC-I expression was correlated with β-2 microglobulin (β2m; $r = 0.7$; $P < 0.001$), but not with T-cell density ($r < 0.32$). The median follow-up for survivors was 9.7 years. High levels of MHC-I expression in tumors concomitant with high T-cell infiltration (CD3, CD4, or CD8) best identified patients with favorable outcomes, compared with patients with one or none of these immune features. The median overall survival (OS) of patients with MHC-I^{hi}CD3^{hi} tumors ($n = 31$) was 116 months compared with 40 months for the others ($P = 0.001$), and the median time to recurrence (TTR) was not reached compared with 17 months ($P = 0.008$). By multivariate analysis, MHC^{hi}CD3^{hi} was associated with OS and TTR independent of the standard clinicopathologic variables. An immune score that combines MHC-I expression and TIL density may be a valuable prognostic tool in the treatment of patients with CLM. *Cancer Immunol Res; 2(6); 530–7. ©2014 AACR.*

Introduction

Individualizing the care of patients with metastatic colorectal cancer based on tumor biology requires biomarkers that estimate a patient's outcome better than what standard clinicopathologic variables accomplish currently. Accumulating evidence suggests that the adaptive immune system can influence cancer progression, and the quantification of tumor-infiltrating lymphocytes (TIL) may improve prognostic staging of patients with solid cancers (1). In this regard, primary colorectal cancer has been the most comprehensively studied tumor (2). A pivotal study of 406 patients with primary colorectal cancer showed that high intratumoral CD3$^+$ T-cell density could identify patients with similar disease-free survival, independent of the depth of tumor penetration (T stage) or nodal metastases (N stage; ref. 3). In addition, the intratumoral T-cell density and quality have been inversely correlated with colorectal cancer progression (4, 5). For instance, the primary tumors of patients with metastatic colorectal cancer to distant organs [tumor–node–metastasis (TNM) stage IV; $n = 86$] harbored two to three times fewer CD8$^+$ T cells and three to five times fewer granzyme B$^+$ T cells than tumors of patients with only regional lymph node metastases (TNM stage I to III; $n = 312$; ref. 5). Although these findings suggest that metastatic tumor deposits represent immune escape variants, we and others have shown that TIL in colorectal cancer liver metastases (CLM) had a prognostic value after complete resection (6, 7) or chemotherapy (8). When considered alone, however, TIL density in CLM seems to be only a modest predictor of clinical outcomes.

Partial or total loss of MHC class I (MHC-I) expression is regarded as a common tumor immune escape mechanism, which theoretically can render cancer cells "invisible" to CD8$^+$ T cells. MHC-I loss has been reported at high frequency in solid tumors (9) and in up to 74% of primary colorectal cancers (10). Conversely, the *HLA* and *β-2 microglobulin* (*β2m*) genes, encoding the MHC constituents, are IFN responsive and their expression can be upregulated in a tumor microenvironment in which productive immune recognition occurs. The prognostic value of MHC-I expression is uncertain in primary colorectal cancer (11, 12), but strong MHC-I tumor expression combined with high CD3 TIL density has been associated with modestly longer disease-specific survival compared with patients with either feature alone (72.5, 68.0, and 69.9 months, respectively; refs. 11, 13).

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The aim of this study was to analyze whether prognostic immune scoring in metastatic colorectal cancer could be improved by assessing MHC-I expression in conjunction with TIL quantification in CLM resected with curative intent.

Patients and Methods

Patients

We identified from a prospective database consecutive patients who underwent resection of CLM with curative intent at our institution between 1998 and 2000 (7). Indications for resectability have been described previously (7, 14). Institutional Review Board approval was obtained. We previously developed a clinical risk score (14), which estimates postoperative outcome and has been validated by others (15). To calculate the clinical risk score, a point is given for each of the following clinicopathologic characteristics: node-positive primary cancer, disease-free interval (DFI; time between resection of primary and liver recurrence) <12 months, more than 1 liver metastasis, largest liver metastasis >5 cm, and prehepatectomy serum carcinoembryonic antigen (CEA) level >200 ng/mL.

Immunohistochemistry

Following pathologic review for diagnostic confirmation and exclusion of highly fibrotic or necrotic tumors, tissue microarrays (TMA) were constructed from 188 patients as described previously (7). Cores measuring 0.6 mm in diameter were made in triplicate from paraffin blocks and processed using the ATA-27 automated arrayer (Beecher Instruments). TMA blocks were cut to 5-μm sections, deparaffinized, rehydrated in graded alcohol, and stained with biotinylated secondary antibodies and positive or isotype controls. CD3, CD4, CD8, and Fox3 staining and quantification have been reported separately (7). We used a validated mouse anti-human monoclonal antibody that binds to MHC-I heavy chains, preferentially for the HLA-B and HLA-C molecules, and seven HLA-As (HC-10; provided by Hidde L. Ploegh, Whitehead Institute, Cambridge, MA; 1:1,000; 1 hour; refs. 16, 17). The polyclonal rabbit anti-human antibody reacting to light-chain β2m was used (A0072; DAKO; 1:50,000; 1 hour). Automated staining was done on a Ventana XT with the OmniMap DAB Detection System (Roche). Nuclei were counterstained with hematoxylin. High-resolution TMA digital images were acquired on a MIRAX SCAN (Carl Zeiss) and quantification was carried out with the Metamorph Image Analysis Software (Molecular Devices) blinded to clinical data. The areas of positive signal and the total area of the tissue core were calculated on the basis of color, where pixels with identical RGB (red, green, and blue) values were grouped together, to calculate a ratio of positive brown staining (moderate to strong) over total staining (all brown and hematoxylin blue) for each core (Supplementary Fig. S1). Thresholds were set to avoid connective tissue, fat, and necrosis. Mean ± SE was calculated per tumor replicate. Quantification of MHC-I on full cores was compared with quantification on zones of tumors excluding stromal bands and necrotic areas, and found to be similar and highly correlated (Spearman $r = 0.993$; $P < 0.001$; Supplementary Table S1). Patients were excluded from the analysis when at least one tumor core could not be quantified for MHC-I expression.

Statistical analysis

Patient disease status was updated through April 2013. Overall survival (OS) and time-to-recurrence (TTR) were calculated from the time of hepatectomy by the Kaplan–Meier method. Groups were compared by the log-rank test. The association between immune parameters and outcome was also evaluated by univariate Cox regression on continuous variables, and using optimal cutoff points selected by the maximally selected χ^2 method (R version 2.7; www.r-project.org) to estimate the best separation between groups with P values corrected for overfitting (7, 18). Forward selection stepwise multivariate Cox regression models were applied to the $MHC^{hi}CD3^{hi}$ immune score and significant clinicopathologic prognostic factors. The Spearman r test was used to assess the correlation between continuous variables, and the Pearson χ^2 test for the association between categorical variables. A two-sided P value of ≤ 0.05 was considered statistically significant (SPSS version 21).

Results

Clinicopathologic features

For this study, we have identified 188 patients with CLM, who underwent partial hepatectomy with curative intent at our institution; samples from 158 of these patients were analyzed after those from 20 patients were excluded for lack of quantifiable cores, 8 for inadequate follow-up, 1 for palliative resection, and 1 for duplicative sample. The median age at hepatectomy was 63 years, and 57% were male. The median follow-up time was 42 months overall and 116 (41–171) months for survivors. At the last follow-up, there were 35 patients (22%) alive without disease, 106 patients (67%) had cancer recurrence, and of the 114 patients (72%) that died 84% of the deaths were from the cancer. The median OS was 46 months. The 5- and 10-year predicted survival rates were 39% and 24%, respectively. The median TTR was 20.4 months. The 5- and 10-year predicted recurrence-free survival rates were 30% and 25%, respectively. Clinicopathologic variables significantly associated with longer OS and TTR (Table 1) were resection margins clear of cancer, and most components of the clinical risk score (14). By these conventional criteria, the longest median OS and TTR were 77.4 and 31.4 months for the 53 patients (34.6%) with the lowest clinical risk scores (0 or 1).

Immunologic features

MHC-I and β2m expressions in CLM were quantified to obtain the percentage of expression per tumor core (Supplementary Fig. S1). The distribution of MHC-I expression across CLM ranged uniformly from undetectable to high levels (range, 1.4%–92.3%; median, 47.7%; terciles, 32.1% and 65.0%; Fig. 1A). This broad distribution allowed the use of terciles as cutoff points to group patients by null/low, moderate, or high MHC-I expression level. The specificity of MHC-I detection was supported by strong correlation with β2m expression ($r = 0.69$; $P < 0.001$); however, the β2m distribution was skewed toward the lower values (range, 1.0%–84.8%; median, 20.9%; terciles, 13.1% and 32.7%; Fig. 1A). The imperfect correlation between MHC-I and β2m was consistent with the preferential binding of HC-10 to HLA-B and HLA-C heavy chains free of β2m (16, 17).

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Table 1. Univariate analysis of clinicopathologic and immune characteristics for survival and recurrence

				OS		TTR	
Variables	**Cutoff**	***n***	**(%)**	**(months)**	***P***	**(months)**	***P***
Clinicopathologic							
Age, y	>63	79	50	40.3	0.06	17.5	0.03
	≤63	79	50	50.6		18.5	
Gender	Male	90	57	42.7	0.9	18.5	0.6
	Female	68	43	45.6		17.7	
Site of primary cancer	Colon	101	64	40.3	0.2	16.8	0.9
	Rectum	57	36	50.1		21.2	
Perioperative chemotherapy	Yes	139	89	45.6	0.8	17.7	0.5
	No	17	11	36.9		59.9	
Major resection (≥3 segments)	No	66	42	55.0	0.02	16.9	0.09
	Yes	92	58	38.5		27.1	
Cancer at resection margin	Negative	141	91	49.5	<0.001	18.8	0.04
	Positive	14	9	19.6		10.1	
No. of hepatic metastases[a,b]	Solitary	79	50	53.0	0.008	22.5	0.05
	>1	79	50	37.4		15.7	
Size of largest tumor, cm[a]	≤5	106	67	53.7	0.003	21.7	0.13
	>5	52	33	33.3		15.0	
Preoperative CEA, ng/mL[a]	≤200	125	85	50.0	0.001	19.0	0.002
	>200	22	15	26.6		10.4	
Node-positive primary[a]	No	52	33	67.8	0.005	46.0	0.002
	Yes	106	67	41.2		15.9	
DFI, mo[a]	≥12	88	56	53.7	0.04	22.5	0.07
	<12	70	44	39.6		15.8	
Clinical risk score	0 or 1	53	35	77.4	<0.001	31.4	<0.001
	2	48	31	50.6		21.4	
	≥3	52	34	26.6		10.2	
Immune features[c]							
MHC-I	High	40	25	89.0	0.13	83.7	0.04
	Low	118	75	40.1		21.5	
β2m	High	63	40	53.4	0.64	25.3	0.44
	Low	94	60	40.1		16.9	
CD3	High	36	23	67.1	0.7	18.5	0.97
	Low	118	77	43.7		18.4	
CD4	High	32	21	110.9	0.02	76.9	0.21
	Low	123	79	40.3		17.0	
CD8	High	39	25	89.7	0.09	46.0	0.38
	Low	116	75	40.1		17.0	
Combination of immune features							
MHC-I^{hi}CD3^{hi}	Yes	31	20	115.9	0.001	NR	0.008
	No	123	80	40.3		17.1	
MHC-I^{hi}CD4^{hi}	Yes	30	19	105.7	0.001	NR	0.001
	No	125	81	39.6		16.9	
MHC-I^{hi}CD8^{hi}	Yes	31	20	89.7	0.008	NR	0.02
	No	124	80	40.1		17.0	

NOTE: Log-rank test, median OS and TTR.

Abbreviation: NR, not reached.

[a]Clinicopathologic features used to calculate the clinical risk score.

[b]Only continuous variable significantly associated with OS and TTR at a level of $P \leq 0.05$ (Cox regression).

[c]Optimal cutoff points by the maximally selected χ^2 method, and *P* values corrected for overfitting.

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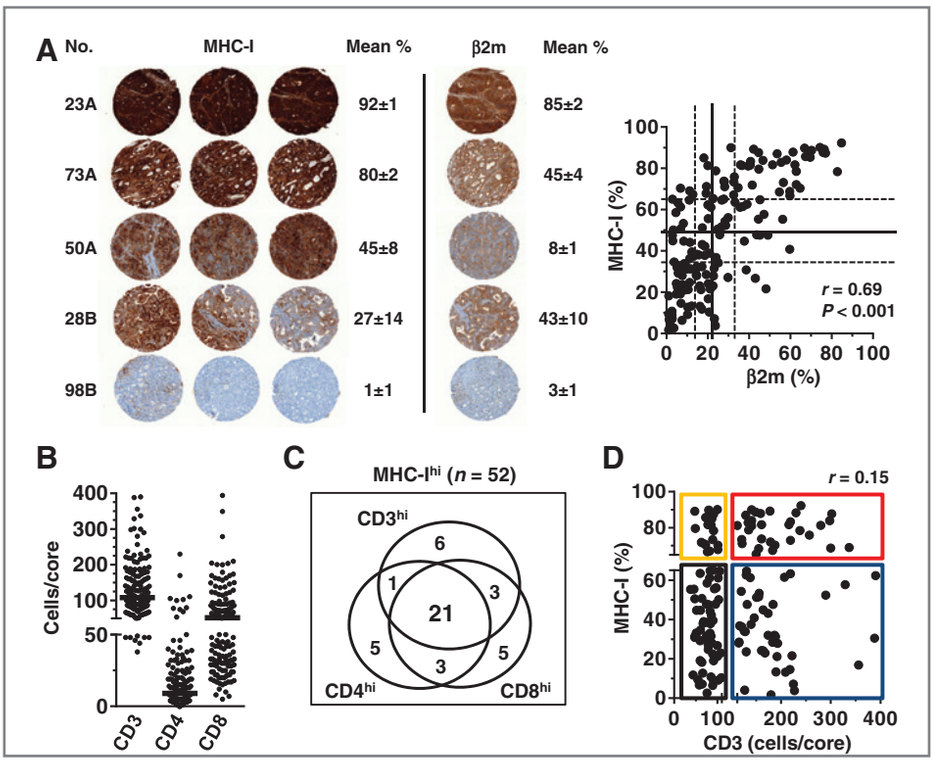

Figure 1. Quantification of MHC-I, β2m, and T-cell subsets. A, representative staining in triplicate of MHC-I expression in 5 patients with CLM, with calculated mean percentage surface expression ± SE. For the same tumors, example of β2m staining of one of the triplicate cores is shown. Correlation of MHC-I and β2m expression is shown. Solid and dotted lines represent median and terciles, respectively (MHC-I, 32%, 48%, and 65%; β2m, 13%, 21%, and 33%). B, quantification of intratumoral CD3 ($n = 154$), CD4 ($n = 155$), and CD8 ($n = 155$) T cells. One dot represents one metastasis (cells/core, mean of replicates). Bars represent medians (109, 9, and 52 cells/core, respectively). One value is out of scale (CD8 = 502). C, within the 52 tumors found to express the highest level of MHC-I (upper tercile), 31 displayed high CD3 infiltration, 80.6% of which represented tumors detected to have high CD4 and/or CD8 infiltration (25 of 31, medians used as cutoff points). D, dot plot representing the absence of a correlation between MHC-I expression and CD3 infiltration. Using the highest tercile as cutoff for high MHC-I expression (broken *Y*-axis, 65%) and the median count for high CD3 infiltration (broken *X*-axis, 109 cells/core), four groups are defined: MHC-I^{hi}CD3^{hi} ($n = 31$, red); MHC-I^{lo}CD3^{hi} ($n = 46$, blue); MHC-I^{hi}CD3^{lo} ($n = 19$, yellow); and MHC-I^{lo}CD3^{lo} ($n = 58$, black). Spearman *r* used for correlation analysis.

Enumeration of T-cell subsets (CD3, CD4, and CD8) infiltrating CLM yielded distributions also skewed toward the lower values (CD3 range, 38–390, median, 109; CD4 range, 0–230, median 9; and CD8 range, 5–502, median 52; Fig. 1B). MHC-I and β2m expression did not correlate with the infiltration of the T-cell subsets (Spearman $r < 0.32$; Supplementary Table S1), supporting that MHC-I was measured mainly on cancer cells and did not simply reflect intratumoral T-cell infiltration.

Weak prognostic value of individual immune parameters

Optimal cutoff values that best separated groups of patients by OS and TTR were calculated for MHC-I (71%), β2m (27%), CD3 (174 cells), CD4 (26 cells), and CD8 (89 cells; Table 1, middle). Individually, MHC-I and CD4 seemed to be the most prognostic immune parameters, but were not robustly associated with both longer OS and TTR. Similar trends were obtained when analyzing immune parameters as continuous variables, but none reached statistical significance at a level of 0.05 (not shown). The prognostic significance of the individual immune parameters thus seemed inferior to the clinicopathologic variables (Table 1).

Combined MHC-I expression and T-cell infiltration defines a subgroup of patients with favorable outcomes

To test the prognostic value of MHC-I expression in CLM in conjunction with intratumoral T-cell density and to avoid overfitting results to the studied population, inclusive thresholds were chosen to define groups by immune parameters rather than optimal cutoffs. MHC-I^{hi} tumors were designated on the basis of the expression above the upper tercile (65%), and high T-cell infiltration was defined by a cell count above the median for a given T-cell subset.

The longest median OS was 116 months, noted in the 31 patients (20.1%) with MHC-I^{hi}CD3^{hi} tumors compared with 40 months for patients with one or none of these immune features ($P = 0.001$), and the median TTR was not reached for the MHC-I^{hi}CD3^{hi} group compared with 17 months for the others ($P = 0.008$; Table 1, bottom). The 5- and 10-year OS rates for patients with MHC-I^{hi}CD3^{hi} tumors were 67% and 49%, respectively, compared with 33% and 19% for all other patients ($P = 0.001$). Recurrence was seen in 41.9% of patients with MHC-I^{hi}CD3^{hi} tumors compared with 73.2% for the other patients ($P = 0.001$).

Because MHC-I^{hi}CD3^{hi} tumors captured most of the MHC-I^{hi}CD4^{hi} and MHC-I^{hi}CD8^{hi} tumors (Fig. 1C), similar

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associations were observed with OS and TTR for these other patient subgroups (Table 1). The prognostic value of β2m expression combined with the infiltration of T-cell subsets was better than either β2m, CD3, CD4, or CD8 alone, but it could not discriminate patients with favorable outcomes as well as MHC-I combined with T-cell quantification did (not shown).

We next assessed the outcomes for the four groups that could be defined on the basis of MHC-I expression and CD3 T-cell infiltration (Fig. 1D). Patients with MHC-I^{hi}CD3^{hi} tumors

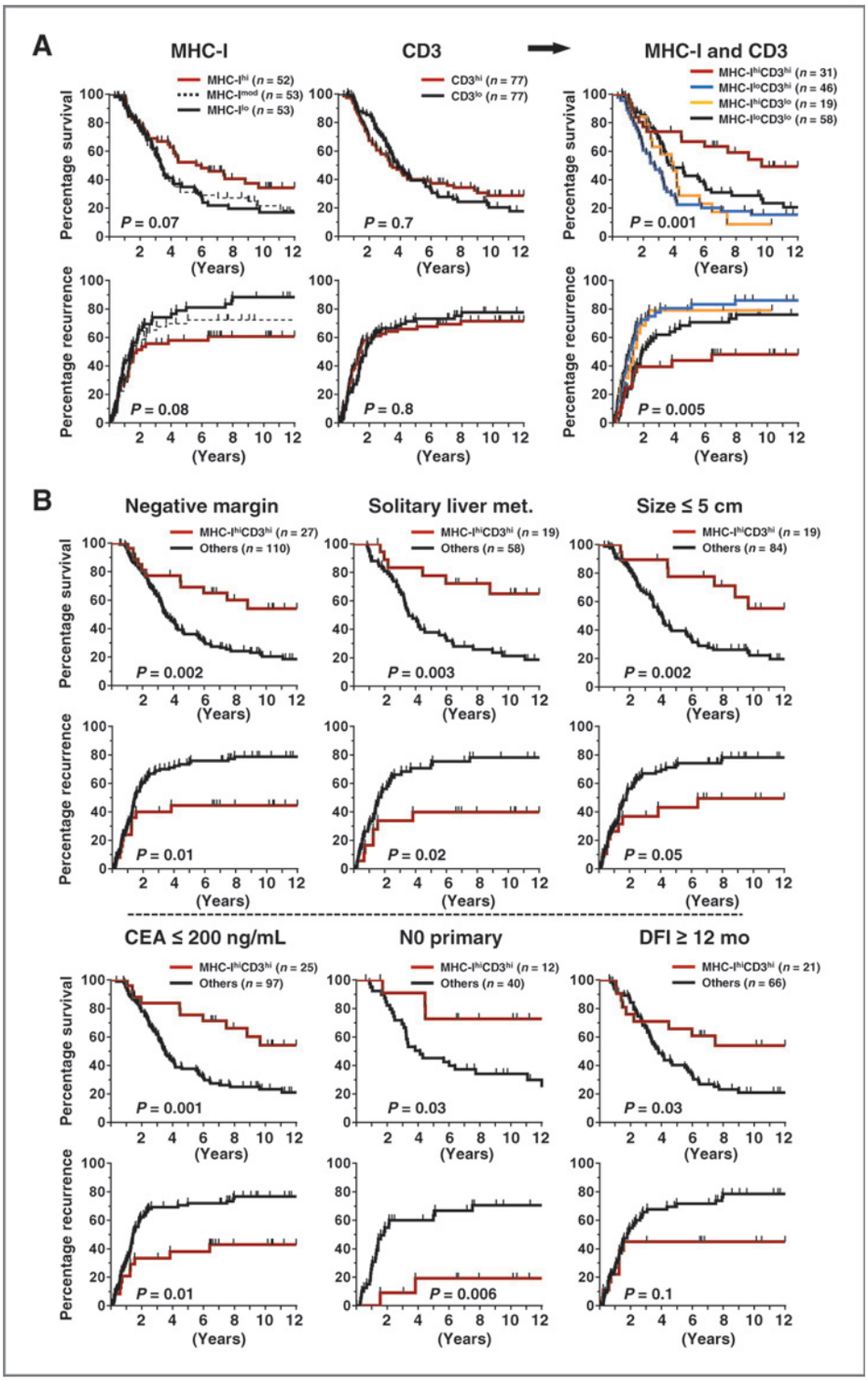

Figure 2. Prognostic impact of MHC-I expression and CD3 T-cell infiltration. A, association between MHC-I expression and CD3 infiltration alone and combined with OS (top) and TTR (bottom) in the entire patient cohort. For MHC-I alone, outcomes are displayed for groups trichotomized on the basis of tercile. For CD3, outcomes are displayed using the median count as cutoff. For the combination of MHC-I and CD3, four groups are displayed and color coded: MHC-I^{hi}CD3^{hi} (red); MHC-I^{lo}CD3^{hi} (blue); MHC-I^{hi}CD3^{lo} (yellow); and MHC-I^{lo}CD3^{lo} (black). B, impact of favorable tumor immune features (MHC-I^{hi}CD3^{hi}, red) on OS (top) and TTR (bottom) in patient subgroups according to clinicopathologic features associated with better prognosis. Log-rank (Mantel–Cox). Met, metastasis; N0 primary, absence of cancer cells in mesenteric lymph nodes draining the primary tumor.

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had the longest median OS and TTR (116 months and not reached, respectively) compared with those of patients with MHC-$I^{lo}CD3^{lo}$ tumors (47 and 23 months, respectively), MHC-$I^{lo}CD3^{hi}$ (33 and 17 months, respectively), or MHC-$I^{hi}CD3^{lo}$ (47 and 16 months, respectively; Fig. 2A).

High MHC-I and CD3 is a prognostic factor independent of clinicopathologic characteristics

There was no correlation between MHC-$I^{hi}CD3^{hi}$ tumors and other clinicopathologic variables (Supplementary Table S2). The MHC-$I^{hi}CD3^{hi}$ immune score stratified patients with better outcomes after grouping by favorable clinicopathologic prognostic factors (Fig. 2B). For example, among the 52 patients with a node-negative (N0) primary tumor, the median OS of patients with MHC-$I^{hi}CD3^{hi}$ liver metastases was not reached compared with 49.5 months for the other patients. Multivariate analysis further supported the MHC-$I^{hi}CD3^{hi}$ immune score as a significant prognostic factor, independent of the clinicopathologic characteristics considered individually, or grouped into the clinical risk score (Table 2). In the 53 patients with a favorable clinical risk score of 0 or 1, patients with MHC-$I^{hi}CD3^{hi}$ tumors fared better with 10-year OS and recurrence-free survival rates of 75% and 67%, respectively (Supplementary Fig. S2). Thus, the MHC-$I^{hi}CD3^{hi}$ immune score still could stratify patients with good prognosis within the clinical risk score, but not those with aggressive disease (clinical risk score $\geq$ 3), 84% of whom had died and 90% recurred at 5 years after CLM resection (Supplementary Fig. S2).

Discussion

Patients with CLM have heterogeneous clinical outcomes. By measuring immune features in CLM resected with curative intent, we identified a subgroup of MHC-$I^{hi}CD3^{hi}$ patients (20% of the cohort) who had a median OS of 9.7 years and a risk of cancer recurrence at 10 years of 48%. The MHC-$I^{hi}CD3^{hi}$ immune score was prognostic of OS and TTR independent of other parameters. This immune score further stratifies outcomes in patients with favorable clinicopathologic features.

Partial or complete loss of MHC-I has been reported in 63% of melanoma, 89% of breast cancer, and 90% of prostate tumors (9). Altered MHC-I expression in primary colorectal tumor was found in 74% of 95 patients (10), but the prognostic value has shown mixed results. Typically, the association between MHC-I expression and the patients' disease outcomes can be nonlinear, given that both strong expression and complete loss of MHC-I molecules can be associated with better prognosis (11). This apparent paradox may be explained by the particular susceptibility of tumor cells lacking HLA surface molecules to natural killer (NK)–cell cytotoxicity mediated by a lack of ligands for the killer-cell inhibitory receptors ("missing-self" hypothesis; refs. 19, 20). It is noteworthy that in addition to T cells, high NK-cell infiltration in primary colorectal cancer has been associated with longer OS and disease-free survival in 157 patients (21). Interestingly, we found that patients with $MHC^{lo}CD3^{lo}$ CLM tended to have better outcomes than patients with $MHC^{hi}CD3^{lo}$ or $MHC^{lo}CD3^{hi}$ CLM [median OS 46.6 vs. 37.4 months ($P = 0.04$) and median TTR 23 vs. 14 months ($P = 0.02$)]. To our knowledge, no studies have tested the prognostic value of concurrent NK-cell infiltration and (lack of) MHC-I expression in colorectal cancer.

Our results indicate that the MHC-$I^{hi}CD3^{hi}$ immune score provides a better discriminatory capacity in CLM compared with its prognostic value when measured in primary colorectal cancer (11, 13). Notably in these studies, 53% of primary tumors assessed in 422 patients had early-stage tumors confined to the colon, 33% had nodal positive cancer, and only 12% had metastasis. In contrast with studies in CLM, the prognostic value of T-cell infiltration alone in early-stage colorectal cancer is strong (22) and may simply outweigh significant additional discriminatory value for MHC-I. Alternatively, because

Table 2. Multivariate analysis of clinicopathologic and immune characteristics for survival and recurrence

	OS		TTR	
Variables	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Model 1				
Minor resection (<3 segments)	0.62 (0.39–0.98)	0.04		NS
Negative margin	0.30 (0.15–0.60)	0.001		NS
Solitary hepatic metastasis		NS		NS
Size of largest tumor $\leq$5 cm	0.47 (0.29–0.76)	0.002		NS
Preoperative CEA $\leq$200 ng/mL	0.50 (0.29–0.85)	0.01	0.46 (0.27–0.78)	0.004
Node-negative primary	0.38 (0.24–0.62)	<0.001	0.52 (0.33–0.81)	0.004
DFI >12 mo		NS		NS
MHC-$I^{hi}CD3^{hi}$	0.36 (0.20–0.67)	0.001	0.54 (0.29–0.98)	0.046
Model 2				
Clinical risk score <3	0.37 (0.25–0.55)	<0.001	0.43 (0.28–0.64)	<0.001
MHC-$I^{hi}CD3^{hi}$	0.45 (0.26–0.79)	0.005	0.52 (0.29–0.94)	0.031

NOTE: Forward selection stepwise multivariate Cox regression.
Abbreviation: NS, not statistically significant.

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metastases theoretically may harbor more immune escape variants than primary tumor, the persistence of strong MHC-I expression in CLM could represent a particularly favorable tumor biology, or detection at an earlier time point in disease progression.

Because 89% of patients in our study received perioperative chemotherapy, another interpretation of our results could be that $MHC^{hi}CD3^{hi}$ in CLM is a surrogate for favorable response to adjuvant chemotherapy. Indeed, growing evidence suggests that the efficacy of some chemotherapeutic agents can be immune mediated and may not entirely result from direct cytotoxicity (23). Most studies testing the value of adaptive immune signatures to predict response to chemotherapy have been performed in breast cancer. On the basis of 89 breast cancer biopsies obtained from women with locally advanced tumors before the initiation of neoadjuvant chemotherapy, several immune-related genes, such as *CD3ζ* chain, *HLA.DPB1*, and *β2m*, were in the top third of genes most closely associated with pathologic complete response (24). Furthermore, MHC-I expression has been associated with improved recurrence-free survival only for patients with breast cancer treated with adjuvant chemotherapy (25). Finally, in patients with unresectable CLM, high levels of CD3/CD8/granzyme-B–positive cells at the normal liver/CLM interface had a sensitivity of 79% to predict response to chemotherapy, whereas the absence of such a favorable immune profile was 100% in predicting nonresponse to chemotherapy (8).

Although our findings are retrospective and require external validation with standardization of MHC-I expression and TIL quantification, they suggest that an immune score that combines MHC-I expression and TIL density may be a valuable prognostic tool in the treatment of patients with CLM. This prognostic tool may also apply to other advanced solid malignancies. Our findings are limited by the fact that the HC-10 antibody detects only a minority of HLA-A alleles. Further studies are necessary to draw firm conclusions about the prognostic value of HLA-A–specific expression. Our results provide an additional rationale to test whether an immune-based signature can predict benefit from adjuvant chemotherapy after complete resection of CLM. As anticancer immune modulation with monoclonal antibodies (e.g., anti-CTLA4 and anti-PD1) begins to show efficacy in a variety of metastatic cancers, MHC expression by tumors may also be evaluated as a predictive marker of response to immunotherapy. Conversely, strategies to restore MHC expression may be pursued to expand the number of patients who could potentially benefit from T cell–based cancer immunotherapy.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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