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Tumor Immune Infiltrate and Response to Chemotherapy

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Mini Review

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Abstract

Chemotherapeutic agents are developed and used for their cytotoxic properties. Emerging evidence suggest that the efficacy of at least some of them is dependent on immune cells present within tumor and its microenvironment prior to chemotherapy as well as changes induced by chemotherapy. Type, number and density of immune cells are found to have prognostic and predictive value. Their evaluation can provide better prognostication compared to conventional methods.

Keywords: Immune infiltrate; Chemotherapy; Immunoscore; Cancer; T lymphocyte; Macrophage; CD8+ T cells

Abbreviations: CTLs: Cytotoxic T Lymphocytes; TII: Tumour Infiltrating Immune Cells; UICC: Union for International Cancer Control; HER2: Human Epidermal Growth Factor Receptor 2; HR: Hazard Ratio; OS: Overall Survival; DFS: Disease Free Survival; RFS: Relapse Free Survival; pCR: Pathogenic Complete Response.

Introduction

Chemotherapy is one of the main pillars of cancer management. Chemotherapeutic agents are developed for their cytotoxic efficacy based on in-vitro data. Progress in understanding of its in vivo efficacy suggest that immune mechanism play an important role in their in vivo efficacy e.g. response to anthracyclines needs an intact immune system [1,2]. Anthracyclines are not effective in immunodeficient mice. Efficacy of cytotoxic chemotherapeutic agents depends on increased vulnerability of rapidly proliferating cells compared to normal cells. Hematopoietic cells are also rapidly dividing cells and are vulnerable to killing by chemotherapeutic agents. Following chemotherapy, they reach nadir and then recover. Failure to recover manifests as myelosuppression and lymphopenia. This has led to a notion that chemotherapeutic agents are immunosuppressive. However chemotherapy is known to boost immune response by activation of immune effector cells (direct immunostimulation) as well as by inhibition of immunosuppressive cell populations (indirect immune stimulation) [3-5] as demonstrated by recent preclinical and clinical studies. The studies reveal potential of chemotherapeutic agents to generate tumor specific adaptive immune response [3,6]. Boosting of immune response is facilitated by recovery following nadir. This provides opportunity to reset the immune system by favouring the rebound replenishment of selected immune cell subsets [7], leading to preferential depletion of immunosuppressive cells, and emergence of a specific effector cell type with anticancer activity [6]. Tumor infiltrating Treg and myeloid derived suppressor cells are major immunosuppressive cells and this population reduces following chemotherapy [4,8-10].

Interaction of chemotherapeutic agents with tumor microenvironment also facilitates it. There is increased intratumoral infiltration of activated immune cells [3-5].

Chemotherapy also induces expression of surface proteins like tumor associated antigens, MHC class-1 proteins, ICAM-1, FAS and mannose-6-phosphate receptors [5,11-13]. Such phenotypic changes make tumour cells more vulnerable to killing by immune cells.

Chemotherapy induced tumor infiltration by CD8+cytotoxic T lymphocytes (CTLs) or the activation of an interferon (IFN) response are associated with improved outcome in various tumors like breast , lung , colorectal carcinoma [4,14-17].

Clinical studies also demonstrate synergistic interaction with chemotherapy and immunotherapy. For instance, CADI-05 and pembrolizumab has been shown to improve the efficacy of platinum doublet in non-small cell lung carcinoma and small cell lung carcinoma [18-21].

T lymphocytes (including its subtypes) as tumor infiltrate are studied extensively. T lymphocytes are designated as CD4, CD8, Treg etc. based on protein expressed on their surface. Their type, density and site are evaluated in Immunoscore. Immunoscore is found useful in predicting outcome in surgically resected tumors [17,22-26]. It has established its value in early stage colorectal cancer undergoing surgical resection [27-29] and is found better than conventional TNM classification including histopathological evaluation. Other cells evaluated include macrophages, NK cells which represent innate immune response. The role of tumour immune infiltrate is currently pursued actively for prognostication and prediction of outcome following chemotherapy. In this mini review information related to role of immune infiltrate as a prognostic and predictive biomarker for response to chemotherapy in human clinical studies is reviewed.

Tumor Immune Infiltrates as a Prognostic Biomarker for Response to Chemotherapy

Outcome of chemotherapy are variable and different, in spite of identical phenotype and histological features. This can be explained, atleast in part, by density, type and site of tumour infiltrating immune cells (TII). From studies done so far, it emerges that prognosis of therapy can be better predicted by residual immune activation present in the tumour at the time of diagnosis. Th1 type of cell mediated immune response is strongly associated with improved survival in many human cancers [1] including breast carcinoma patients [30,31]; paediatric medulloblastoma patients [32]; gastric cancer patients who underwent curative gastrectomy [33]; colorectal cancer patients [34-36] and ovarian carcinoma patients [37,38]. The development of Th2 responses has been associated with worsened outcomes in pancreatic cancer patients [39].

In general, infiltration by CD8+ T cells is associated with better prognosis and Treg is associated with poor prognosis [1]. Majority of outcome studies are based on neoadjuvant or adjuvant settings as it provides adequate amount of tissues.

Following section provides an overview of immune infiltrate as a prognostic biomarker in various cancers.

Colorectal Carcinoma

Besides Th1 type of immune response, number of tumor infiltrating CD8+ T cells are associated with a better prognosis [14,27,28,40,41]. Union for International Cancer Control (UICC) staging can be divided to subgroups based on amount of TII. Higher TII has a better prognosis while lower TIL has a worse prognosis [29]. Highest immunoscore (higher CD8 and CD45RO cells) with lower tumor recurrence (4.8%) and better survival 86.2% at five years compared to lowest immunoscore with higher tumor recurrence(75%) and 27.5% survival at five years [27].

Immune score is significantly associated with differences in disease-free, disease-specific, and OS (hazard ratio [HR], 0.64, 0.60, and 0.70, respectively; $P < .005$). It is also found better than histopathological features in predicting recurrence as well as survival. Cox multivariate analysis supports the advantage of the immune score (HR, 0.64; $P < .001$; $C\tau = 67.9\%$) [42].

NK cell infiltration also has a prognostic value. Higher infiltrating NK cell have better five year survival compared to tumors with lower infiltrating NK cells in spite of same TNM staging of disease ($P < 0.001$) [43].

Over expression of CD73 is associated with poor prognosis [44,45].

Tumor infiltrating high FOXP3:CD4 ($p = 0.03$) and FOXP3:CD8 ($p = 0.05$) ratios are associated with shorter OS [46].

Non-Small cell Lung Cancer

Higher CD3+, CD8+, CD4+ and TII indicate favourable prognosis and Treg with poor survival [46]. Higher ratio

of FOXP3+ to CD3 also has a higher risk of relapse [47]. Concomitant high CD8+ and CD4+ T cell infiltration is an independent favourable prognostic factor for OS [40,48]. Similarly density of mature dendritic cells is associated with OS and DFS, constituting an independent prognostic factor [40,49].

M1 macrophage infiltrate also has prognostic value with 5 year survival >75% for patients with higher than median values and <5% for lower values [50].

Increased in filtration of follicular B cells also have a prognostic value and its combination with mature DC identifies patients with better prognosis across all stages of NSCLC [51].

Breast Cancer

In triple negative and human epidermal growth factor receptor 2 (HER2) +ve breast cancer, higher TII is associated with better outcome [52]. Tumour infiltration by T cells has a favourable prognostic impact in HER2 +ve and estrogen receptor (ER) -ve cancers [40,53] and triple negative breast cancer(TNBC) [54, 55], however infiltration with γδ T cell is associated with poor prognosis , tumor spread and lower survival [56]. In patients with TNBC every 10% increase in stromal Tumor-infiltrating lymphocytes (TILs), is associated with a 14% reduction of risk of recurrence or death (p = 0.02), 18% reduction of risk of distant recurrence (p = 0.04), and 19% reduction of risk of death (p = 0.01) were observed [55]. Elevated CD73 expression in breast cancer predicts a good prognosis [57] except in TNBC [58].

Intratumoral (It) -TII and Stromal (Str) -TII had prognostic value for metastasis-free survival [Hazard Ratio (HR) 0.86, 95% (Confidence Interval) CI 0.77–0.96; P = 0.01 and HR 0.85; 95% CI 0.75–0.98; P = 0.02 for Str-TII and It-TII, respectively] and OS(HR 0.86; 95% CI 0.77–0.97; P = 0.01 and HR 0.86; 95% CI 0.75–0.99; P = 0.03 for Str-TII and It-TII, respectively) [59].

The 5 year OS rate was 91% (95% CI 68% - 97%) for High-TIL patients and 55% (95% CI 48% - 61%) for Low-TIL patients (HR 0.19; 95% CI 0.06–0.61, log-rank P = 0.0017) [59].

1. TIIs (low, intermediate, and high) proved to have significant prognostic value (p = 0.015) regarding relapse free survival (RFS) in TNBC (p = 0.097) but not among HER2+ve breast cancer treated with chemotherapy. The prognosis was also significantly poor in TNBC patients in the low-TII group compared with the intermediate/high-TII groups (HR: 2.49; 95 % CI: 1.05–5.55) [60].
2. With every 1% increase in TIIs there was a 3% decrease in the rate of an event (adjusted HR, 0.97; 95% CI 0.95-0.99; P = 0.002) across all treatment groups [61].
3. The risk of death was reduced by 15% and 11% for each 10% It-TII and Str-TII increment, respectively (HR 0.85; 95% CI 0.77– 0.95; P = 0.003 for It-TII; HR 0.89; 95% CI 0.81–0.96; P = 0.005 for Str-TII) [62].

Clear Cell Renal Cell Carcinoma (CC RCC)

Infiltration with CD8+ T cells in primary and metastatic sites in clear cell carcinoma is associated with poor PFS and OS [63]. This may be due to PD-1 expression and coincident PD-L1 expression on tumor [64]. CC RCC also express PD-1, LAG-3 and suggest poor outcome [64,65].

Ovarian Cancer

Infiltration of tumour with CD4+T cells is associated with better prognosis in non-serous ovarian cancer and CD8+ cells in advanced clear cell carcinoma [66]. A high ratio of CD8+ over FOXP3+ TIIs is also a positive prognostic factor for OS [67]. In adjuvant setting, use of platinum based chemotherapy is associated five year OS rate of 73.9% in patients having T cell infiltration compared to 11.9% for patients with absence of T cell infiltration. (P<0.001) [67].

Resistance to platinum-based therapy is associated with a significantly lower intraepithelial CTL infiltration [χ^2test; positive vs. negative: 9.0% vs. 97.7%; P < 0.001)]. With a low CTL infiltration rate as an independent factor of platinum resistance (Odds ratio (OR), 3.77; 95% CI, 1.08-13.12; P = 0.037) [66].

Over expression of CD73 in epithelial ovarian carcinoma is also associated with a better prognosis [68] with 5 year OS of 73% compared to 50.1% %; p=0.023 for CD73 negative [68]. Higher M1/M2 ratios of TAM (Tumor-associated macrophages) are also a better prognostic parameter [69].

Melanoma

TIIs have a positive prognostic value on OS in primary cutaneous melanoma [70] with reduced potential for metastasis [71]. TII also prognosticate DFS. The difference in DFS between group with highest TII and absent TII was found to be 52% at thirty months (p = .007) [71].

Hepatocellular Carcinoma

A high ratio of activated CTLs (Granzyme B+) over Treg (FOXP3+) has a positive prognostic impact on OS and DFS [72].

Uroepithelial Carcinoma

A high frequency of CD8+ TII is a positive prognostic factor for OS [73].

Oropharyngeal Cancer

In HPV positive oropharyngeal cancers, Higher TII is associated with better prognosis (HR0.28; 95% CI 0.13–0.62; P= 0.002) [74].

Tumor Infiltrating Immune Cells as Predictive Biomarkers for Efficacy of Chemotherapy

Besides prognostication, TII is also found useful in predicting response to chemotherapy. Activated CD4+ T cells are known to improve efficacy of chemotherapeutic agents in a dose dependant manner [75]. Chemotherapeutic agents vary in their effects on immune cells as described in previous section. Predictive value of TII depend their base line value (type, density and location) as well as changes brought about by therapy. Majority of such observations are made through studies in neoadjuvant and adjuvant settings as it provides adequate opportunities for evaluation. The predictive value based on neoadjuvant and adjuvant setting should be considered as a trend for advanced metastatic cancer as they have significantly higher immunosuppression. Following section provides overview of immune infiltrate as predictive biomarkers for efficacy of chemotherapy in various cancers.

Breast Cancer

Baseline Predictor of Better Prognosis

Following immune parameters at pre-treatment biopsy predict better outcome:

1. TIIs for neoadjuvant anthracycline-based therapy in all breast cancer [15,76,77] except hormone receptor negative [77].
2. Major histocompatibility complex(MHC) class-I staining of tumor cells and FOXP3+ staining of T cell infiltrates predict improved progression free survival (PFS)with systemic cyclophosphamide based chemotherapy (P = 0.013) [78].
3. HER-2 +ve breast cancer:
   a) TII predicts response to non anthracycline based adjuvant therapy [79].
   b) In metastatic breast cancer, treated with trastuzumab, FcγR2A-131 H/H; FcγR3A-158 V/V, both single nucleotide polymorphisms predict clinical responses and PFS [80].
   c) In a triple negative HER-2 positive breast cancer, each 10% increase in TIIs predicts increased distant DFS with hazard ratio 0.77 (95% CI, 0.61-0.98 ; p = 0.02) [54].
4. Significantly higher numbers of TII [CD3+, CD8+, and FOXP3+ T cells] were observed in the high grade tumors, tumors of positive nodal status, and tumors negative for hormone receptors [81].
5. TII count predicts pathological complete response (pCR) (OR, 4.77; 95% CI, 1.05–21.6;p = 0.043)[82].
6. High CD8+ TII predicts better outcome with anthracycline-based therapy. (HR 0.36; 95% CI, 0.15 to 0.84; P = 0.0177),in HER2+ve and triple-negative tumor phenotypes. TII predict response to anthracycline-based chemotherapy in ER-ve breast cancer [83].
7. High levels of intraepithelial CD3+ TII predicts increased DFS for adjuvant anthracycline based therapy (P = 0.0023) [83].

Baseline Predictor of Poor Prognosis

CD73 expression predicts longer DFS (HR 0.26; 95% CI 0.1-0.66; P=0.0044) and OS(HR 0.24; 95% CI, 0.07-0.85; P=0.027) [57]and chemo-resistance to anthracycline in triple negative breast cancer [58]. Loss of function mutations in TLR4 predicts early relapse following anthracycline based chemotherapy [22,84]. Low level of infiltration by CD4 T follicular helper cells predict poor prognosis in all breast cancer[85] while Lower Th1 gene signature in HER2+ve tumors predict poor outcome [85].

Baseline Predictor of Pathologic Complete Response in Breast Cancer Following Neoadjuvant Therapy

Following baseline immune parameters predict pathologic complete response.

1. Up regulation of genes involved in the immune response (e.g., MCP1, CD68, CTSB, CD18, ILT-2, CD3z, FasL, HLA.DPB1, GBP1) [86].
2. Genes associated with STAT-1, IFN-stimulation predict better outcome [76,87,88]. High levels of CD3+ or CD83+ cells (mature dendritic cells) [89]. High immune module scores were associated with increased pCR probability in all BC subtypes [87].
3. Lymphocyte infiltration with up regulation of transcripts CD3D and CXCL9 [76] predict better outcome.

4. Presence of CD8+, CD4+ cells predict complete pathogenic response to neoadjuvant therapy [81, 82].
5. In the patients receiving trastuzumab, high TII predicts higher was pCR rate [OR, 2.06; 95% CI, 1.21–3.5;P=0.008][90].
6. The predictive value of high CD8+ TIIs for pCR was significant (OR, 34.84; 95% CI, 9.48–127.96, P < 0.001) in a meta-analysis of 13100 cases [91].
7. TIIs greater than 5% predict higher pCR rates independent of treatment group (OR, 2.60; 95%CI, 1.26-5.39);
8. Higher CD8+/CD4+ ratio predicts pCR. (P=0.018).CD8+ TIIs (OR, 9.786; 95% CI, 2.121–45.149; P=0.003) were independent predictive factors for pCR [92].
9. Higher CD8+ TIIs predicts pCR group for anthracycline containing therapy [92].
10. In patients with ER-ve tumors treated with neoadjuvant anthracycline-based chemotherapy, TII predicts pCR (74% TII-high patients vs. 31% TII low patients OR, 6.33; 95%CI, 2.49 to 16.08; P < 0.0001) [83]. Also, identical pCR rates are seen in TNBC.
11. TII is an independent parameter for pCR (OR 6.42; 95% CI, 2.08 to 19.8;P = 0.001), from standard pathologic parameters [83].
12. TNBCs with the high CD8+ TII group for residual tumors compared to low CD8+ TII group had significantly better RFS(73 % vs 30 %; P<0.0001 and HR, 3.09 ;(95 % CI,1.537–6.614; P=0.0013) and breast cancer specific survival (BCCS)(86 % vs 42 %; P<0.0001) [93].
13. TNBCs with a higher CD8/FOXP3 ratio compared with a lower CD8/FOXP3 ratio was also significantly correlated with better five year RFS (72 % vs 40 %; P=0.009) with HR2.07; 95 % CI 1.029–4.436; P=0.0412 and BCSS (77 % vs 56 % P=0.027) [93].
14. High CD8+ TII levels and CD8/FOXP3 ratio in residual tumors could accurately predict the better clinical outcome in TNBC patients with non-pCR following NAC [RFS (73 % vs 30 %; P<0.0001) with HR 3.09; 95 % CI, 1.537–6.614; P=0.0013) and BCSS (86 % vs 42 %; P<0.0001)] [93].
15. Baseline higher TII levels (greater than the median) is associated with identical EFS irrespective of achieving pCR [61].
16. Baseline TII level of at least 40% had excellent 3-year EFS (97%; 95% CI, 88%-99%) regardless of pCR outcome (Only 35% with ≥40% TIIs, achieved a pCR) [61].
17. Group having pCR and high TII has a better prognosis and subgroup with no pCR and low TII tumors has a worse prognosis (P = 0.039) [90].
18. TIIs were significantly related to pCR ratio in TNBC (p = 0.024) (but not in HER2+ve BC (p = 0.30) [60].

Changes Immune Biomarker Following Chemotherapy and Response Prediction

1. Increased TII following chemotherapy predicts pCR to neoadjuvant chemotherapy [15,76] and improved time to tumor recurrence (TTR) and OS to adjuvant therapy [94].
2. Increased CTL / Treg ratio predict pCR to neoadjuvant anthracycline based therapy. It predicts pathological complete response even when such changes are seen after one cycle of anthracycline-based chemotherapy [3,76,94].
3. Increased CTL / Treg ratio predict Improved RFS and OS to neoadjuvant based paclitaxel therapy and TTR and OS adjuvant therapy [94].
4. Increased T-cell cytokine levels (IFN-γ, IL-2, IL-6, and GM-CSF) and decreased inflammatory cytokine levels (IL-1, TNFα) in serum after taxane therapy is associated with better outcome (more pronounced effect with Docetaxel over paclitaxel) [95].
5. High intratumoral levels of CD8+ CTLs at surgery following neoadjuvant paclitaxel-based chemotherapy, correlate with clinical response [96,97].
6. Increased TAM predicts shorter RFS and OS [3,97].
7. High CD8 and low FOXP3 cell infiltrates after chemotherapy predicts improved RFS (p = 0.02) and OS (p = 0.002) as an independent predictor. A combined score associating CD8/FOXP3 ratio and pathological American Joint Committee on Cancer (AJCC) staging identifies a subgroup of patients with a significantly better long term OS (100%). This is also seen in an independent cohort of HER2-ve breast cancer patients [98].
8. TNBCs with a higher increase in CD8+ TII group had a significantly better RFS than those with a lower increase (P=0.011), with the 5year RFS rates 74 % and 20 % respectively [93].
9. TNBCs with a higher increase in CD8/FOXP3 ratio compared to low rate of changes in CD8/FOXP3 hada lower recurrence rate (25 % vs 61%; P=0.0352) [93].
10. Significantly better 5-year RFS (68 % vs 41 %; P=0.011) and BCSS (78 % vs 58%; P=0.023) [93].

HER-2+ve Breast Cancers

1. Advanced breast cancer treated with trastuzumab combined with chemotherapy [99], significant antiHER-2 specific CD4+ T-cell responses; anti-HER2 Igλ antibody responses after trastuzumab therapy is associated with clinical benefit.
2. Decreased Treg numbers after trastuzumab therapy were associated with favorable clinical outcome in HER2 positive (but not HER2 negative) breast cancer [100].
3. Improved outcome following decrease ratio of circulating Treg/Th17 cells after trastuzumab therapy [101].

Colorectal Cancer (CRC)

In rectal cancers, there is a significant correlation between densities of CD3+ and CD8+ cells and the pathological response to neoadjuvant radio chemotherapy [23].

TII predicts survival benefit in CRC treated with 5-fluorouracil (5-FU) based chemotherapy [102,103]. Infiltration of tumor with CD56+ve cells [NK cells] predict response to cetuximab as well as improved PFS [104].

High level of granulocytic myeloid-derived suppressor cells (gMDSC) was associated with a poor prognosis in colorectal cancer treated with 5-fluorouracil (5-FU), oxaliplatin and bevacizumab [105].

In patients treated by surgery alone (n = 851), markers with significant prognostic value included poor histologic grade, T4 stage, N2 nodal status, vascular invasion, and perforation, but not the presence of TIIs [102]. In a metastatic colorectal cancer, TII in tumor as well as metastatic lesion is a better predictor for survival in synchronous metastasis compared to metachronus metastasis (HR 3.696; 95% CI 1.935-7.060; P=<0.001) [24].

Colorectal Cancer with Liver Metastasis

TII densities at the invasive margin of liver metastasis predicts response to chemotherapy with a sensitivity of 79% and specificity of 100%[106]. CD3, CD8 or Granzyme B positive immune cells at the invasive margins of liver metastasis also predict treatment response [29,106] and prolong RFS. Higher TII is also associated with improved RFS (p=0.001) and OS (p=0.0018) [106].

Increased TII following chemotherapy also suggest improved OS [59]. Decreased granulocytic MDSCs following 5-FU, oxaliplatin and bevacizumab is associated with better survival in colorectal cancer [107].

Ovarian Cancer

The presence of intratumoral CD3+ T cells independently predicts delayed recurrence or delayed death following:

I. Platinum based chemotherapy in advanced ovarian cancer with five year OS rate of 38.0% among patients whose tumors contained T cells and 4.5% among patients whose tumors contained no T cells [67].
II. Complete clinical response after debulking and platinum-based chemotherapy with five-year survival rate was 73.9% among patients whose tumors contained T cells and 11.9% among patients whose tumors contained no T cells [67].

Higher CD3+ and CD8+ T cells within stroma also predicts response to platinum based chemotherapy [104] with improved survival following adjuvant chemotherapy in patients with higher CD8+ T cells [3,108].

CD27 subset of CD8+ T cell infiltration is associated with better DFS in adjuvant setting (HR 0.23; 95% CI 0.10–0.56; P= 0.001) [46]. In neoadjuvant setting TII has no prognostic value [46].

Non-Small Cell Lung Cancer (NSCLC)

In adjuvant setting, in stage II and III settings higher CD8+ TII predicts low recurrence rate (p= 0.018) and highest Immunoscore predicts better DFS [25]. Similarly in stage-I disease also are high CD8+TIIs predicts better DFS (HR 0.393; 95% CI 0.217-0.714; P=0.002) and OS (HR 0.505; 95% CI, 0.259-0.982; P=0.044) [109]. In another study involving adenocarcinoma of lung, high CD8+ TII in adjuvant settings were associated with better DFS (HR 0.41; 95% CI, 0.21–0.82; p= 0.012) [110]. CD73 expression protects NSCLC from cytotoxic effects of chemotherapy and predict lack of response to therapy [111].

CD8+TIIs are effective prognostic predictors. High CD8+TIIs are significantly associated with better DFS (HR 0.393; 95% CI, 0.217-0.714; P=0.002). Only CD8+TIIs expression is associated with OS (HR 0.505; 95% CI, 0.259-0.982; P=0.044).

Myeloid derived suppressor cells are immunosuppressive cells. In contrast to CD8+ T cells, their increase in tumor predicts resistance to chemotherapy in NSCLC [47,112,113].

Gastrointestinal Stromal Tumors

Higher TII predicts improved PFS to imatinib based therapy [3,114]. Increased production of IFN-γ by circulating NK cells after imatinib treatment predicts prolonged time to progression [115].

Oropharyngeal

High CD3 and CD8 T cells predict improved PFS and OS [116] to adjuvant therapy.

Biliary Tract Cancer

High TII are associated with improved OS to adjuvant therapy [117]. Therapy can be multimodal [4].

Melanoma

Melanoma is considered an immunological tumor. High infiltrating CTL predict improved OS to adjuvant therapy [118].Tumors with high levels of CD3+ and CD8+ cells around metastases predict improved OS following neoadjuvant and/or adjuvant chemotherapy [3,118].

Rectal Cancer

The density of CD4+ as well as CD8+ T cells was highly correlated with tumor response as well as with the rate of decrease of tumor size following neoadjuvant chemo radiotherapy (P = 0.0013, 0.0020) [119]. Immunoscore was originally designed based on studies involving patients with colorectal cancer undergoing surgical treatment [3,23]. Immunoscore correlates with OS and PFS [23]. CTL predicts improved PFS and OS to neoadjuvant therapy [23].

Pancreatic Cancer

Increased Th2/Th1 ratio predicts shortened OS following adjuvant therapy [39]. High tumor associated macrophages predicts response to Gemcitabine based therapy [120]. Higher CD8+ TII is a predictor of better OS (HR 0.474; 95% CI 0.251- 0.893; P= 0.021) and PFS (HR 0.556; 95% CI 0.313-0.988; P=0.045) [121].

Oesophageal Adenocarcinoma

Higher levels of TIIs in the pathological specimen were associated with significant pathological response to neoadjuvant chemotherapy (NAC). On multivariate analysis increased levels of CD4+ (p = 0.017) and CD8+ TIIs (p = 0.005) were associated with significant local tumour regression and lymph node down staging, respectively [122].

Head and Neck Cancer

High expression of CD3 TII predicts significantly better OS (HR 0.429; 95% CI 0.206-0.895; P= 0.024)and PFS (HR 0.494; 95% CI 0.248-0.982; P=0.044) following definitive chemo radiotherapy. Similarly high CD8+ TII also predicts better OS (HR 0.359; 95% CI 0.130 - 0.990; P= 0.028) and PFS (HR, 0.464; 95% CI 0.198 - 1.087; P= 0.047) [123].

Oropharyngeal Cancer

Higher baseline CD3+ cells predicts better OS following cisplatin based chemotherapy (HR, 0.39; 95% CI 0.21–0.73; P= 0.003) [124].

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