cancers

MDPI

Review

Liver Microenvironment Response to Prostate Cancer Metastasis and Hormonal Therapy

Alison K. Buxton, Salma Abbasova, Charlotte L. Bevan * and Damien A. Leach *

Division of Cancer, Imperial Centre for Translational & Experimental Medicine, Imperial College London, Hammersmith Hospital Campus, London W12 0NN, UK

* Correspondence: charlotte.bevan@imperial.ac.uk (C.L.B.); damien.leach@imperial.ac.uk (D.A.L.)

Simple Summary: Prostate cancer patients with disease that has invaded the liver have the worst outcomes. Within the liver, cancer cells are exposed to a unique microenvironment of liver specific cells and proteins. In general, interaction between the microenvironment and cancer is known to provide cues which alter cancer cell biology and behavior. This review aims to summarize current knowledge about the microenvironment of the liver, what predisposes prostate cancer to move to the liver, how the liver responds to prostate cancer being there, and how the liver responds to current treatment strategies. We aim to provide insight into this under-investigated area of prostate cancer research as if we can understand why liver metastasis is associated with such poor patient outcomes, we will be better placed to address this.

Abstract: Prostate cancer-associated deaths arise from disease progression and metastasis. Metastasis to the liver is associated with the worst clinical outcomes for prostate cancer patients, and these metastatic tumors can be particularly resistant to the currently widely used chemotherapy and hormonal therapies, such as anti-androgens which block androgen synthesis or directly target the androgen receptor. The incidence of liver metastases is reportedly increasing, with a potential correlation with use of anti-androgen therapies. A key player in prostate cancer progression and therapeutic response is the microenvironment of the tumor(s). This is a dynamic and adaptive collection of cells and proteins, which impart signals and stimuli that can alter biological processes within prostate cancer cells. Investigation in the prostate primary site has demonstrated that cells of the microenvironment are also responsive to hormones and hormonal therapies. In this review, we collate information about what happens when cancer moves to the liver: the types of prostate cancer cells that metastasize there, the response of resident mesenchymal cells of the liver, and how the interactions between the cancer cells and the microenvironment may be altered by hormonal therapy.

Keywords: prostate cancer; liver; metastasis; microenvironment; niche; ECM; hormones; androgen

Citation: Buxton, A.K.; Abbasova, S.; Bevan, C.L.; Leach, D.A. Liver Microenvironment Response to Prostate Cancer Metastasis and Hormonal Therapy. *Cancers* **2022**, *14*, 6189. https://doi.org/10.3390/cancers14246189

Academic Editor: Vasiliki Tzelepi

Received: 18 November 2022
Accepted: 13 December 2022
Published: 15 December 2022

1. Introduction

Prostate cancer (PCa) is the fourth most commonly diagnosed cancer globally, with particularly high prevalence in western countries [1]. When confined to the prostate the disease is frequently relatively indolent; problems arise when the disease progresses and moves to other organs, with most PCa-related deaths being due to disease metastasis [2,3]. Developing from the luminal epithelial cells lining the glandular tubules of the prostate, PCa grows into the surrounding stroma, then can invade local surrounding organs (e.g., bladder, seminal vesicles) and lymph nodes, and in advanced cases, metastasizes to distal sites such as bone and/or visceral organs [4,5]. The liver is considered one of the most common sites for metastasis among solid tumors, with liver metastasis occurring in up to 50% of metastatic gastric/colon cancers, between 10–20% of metastatic melanoma cancers, 4–17% of metastatic lung cancer, 30–40% of metastatic pancreatic and 6–38% of metastatic

breast cancers [6,7]. Historically, PCa-associated liver metastases are relatively uncommon—but when they do occur are associated with shorter overall survival times and are less responsive to treatments [8,9].

Since PCa cells proliferate in response to androgens, anti-androgen therapies are commonly the drug of choice for inoperable PCa treatment. These act at the level of the androgen receptor (AR), binding to it and preventing its activation, hence inhibiting androgen-responsive gene transcription [10]. Whilst this approach works well initially in the majority of cases, cancers often become resistant to such hormonal/anti-androgen therapy [11]. This is termed castration-resistant PCa (CRPC), and is associated with elevated levels of serum PSA, confirming progression is still driven by AR signaling as PSA is an AR target gene [3]. Second generation anti-androgens, such as bicalutamide and enzalutamide, are widely employed to more effectively target the AR signaling pathway and manage metastatic cases, but the issue of resistance still remains [12].

Anti-androgen therapies, which are given systemically, have also been associated with other effects in the liver [13], although few papers address this impact. One of the most common adverse effects seen with anti-androgens in the liver is liver injury onset [14]. In response to injury, the liver initiates both inflammation and fibrosis. Damage to the parenchyma causes release of paracrine factors, which recruit immune cells and activate stellate cells, which in turn release a plethora of factors causing recruitment of more immune cells and activated stellate cells, myofibroblasts, neo-angiogenesis, and deposition of a dense extracellular matrix (ECM) [15]. In time this process resolves and liver regeneration occurs, but prolonged damage responses can be detrimental to liver function, and the prolonged fibrotic response can also create a microenvironment or pre-metastatic niche which is favorable/supportive for metastatic seeding and growth [16–20]. Furthermore, in those colorectal and breast cancers that metastasize to the liver, there are several changes associated with ECM interactions that are not seen in tumors that metastasize to different organs [21], indicating that the liver ECM environment may be selective for certain types of metastatic cells.

The vital role of ECM in disease progression is also seen in the primary site [22,23] where in PCa the ECM is known to regulated by AR [24]. AR signaling in the stroma of the microenvironment has been shown to affect cancer cells [25]. Previously, stromal AR was shown to be vital for prostate growth and development, whilst epithelial AR was known to be responsible for the androgen-dependent synthesis of epithelial secretory proteins [26,27]. More recently, AR signaling in the cancer stroma was shown to impact patient outcomes by inhibiting cancer cell invasion, however, the mechanisms behind the roles stromal AR plays in disease progression are not fully understood [24].

The changes to the tumor microenvironment and cells therein highlight its importance in cell invasion and metastasis. The aim of this review is to collate the current knowledge of what types of PCa metastasize there, what happens to the liver when PCa invades, and what associations exist with current therapeutic options.

2. Metastasis to the Liver

The liver is a large organ which primarily filters blood coming from the digestive tract, but also has critical roles in metabolism and secretion. At a microscopic level, the liver is composed of liver lobules, which are roughly hexagonal in shape (Figure 1A). At the outside of each segment of each lobule are hepatic triads comprised of an artery, a vein, and a bile duct. These flow toward the center of the lobule, where there is a central vein. Between the triad and central veins are sinusoids through which the mixed veinous and arterial blood flows, each sinusoid is composed of specialized parenchymal cells called hepatocytes and lined with endothelial cells. Between the parenchymal hepatocyte cells and the endothelial cells is the space of Disse, in which mesenchymal and inflammatory cells reside.

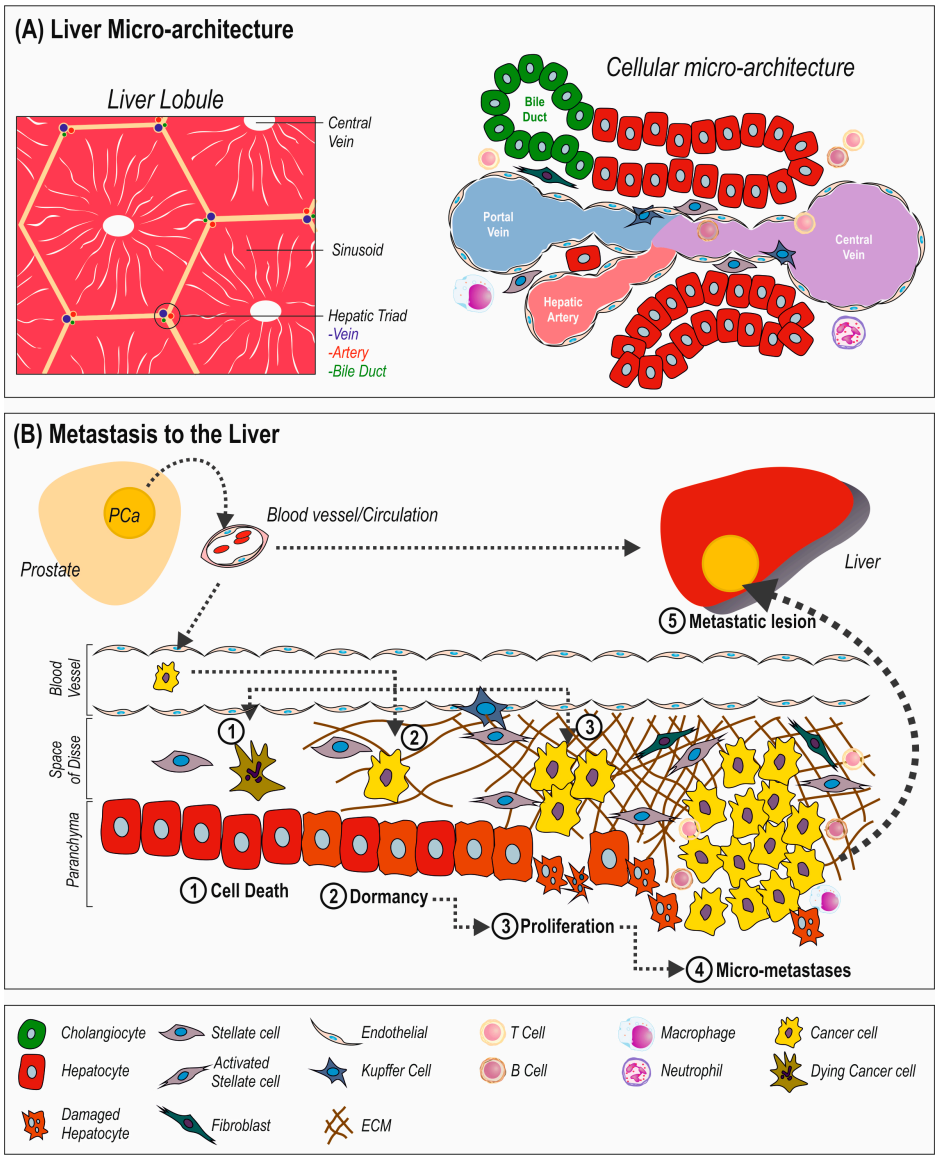

Figure 1. (**A**) Liver Lobule Cellular Microenvironment. The liver is comprised of hepatic lobules, which are the microscopic hexagonal subunits of the liver. These consist of a central collecting vein, hepatocyte lined sinusoids leading to hepatic triads, a collection of three ducts; hepatic artery, portal vein, and bile duct. Between the endothelial cells and either hepatocytes or cholangiocytes/bile ducts, is the space of Disse, a region where mesenchymal cells reside, such as stellate cells, dendritic cells/immune cells, and fibroblasts. (**B**) Metastatic colonization of the liver. Escaping from the primary site, cancer cells invade the circulatory system, through which they navigate to the liver. Once extravasated from hepatic blood vessels and in the liver, cancer cells can undergo cell death or they can remain dormant. From dormancy, cancer cell proliferation can be activated, allow for the formation of micro-metastases, which with continued proliferation become macroscopic metastatic lesions. There is an associated change in the resident cells, with damage to the hepatocytes, increase in ECM due to activation of stellate cells and recruitment of fibroblasts. There is also a potential influx of immune cells.

In the primary site, cancer cells invade through the stroma and escape the primary site via intravasation into the vasculature, where they circulate until they leave the vasculature (extravasation) and colonize the liver. In the liver, cancer cells either undergo cell death, or they can remain in a dormant state, or they proliferate and form micro-metastases until growing enough to become a macroscopic metastatic lesion (Figure 1B).

As previously summarized, many solid tumors metastasize to the liver [6]. In a study of 74,826 PCa patients with metastatic disease, 84% of metastases were found in the bone, whilst liver metastasis accounted for 10.2% [28]. In a retrospective analysis of the SEER dataset, liver metastasis occurred in around 3% of metastatic PCa (20,034 men, [29]), whilst in clinical trials for advanced disease, liver metastases account for between 12–30% [30,31].

3. Prostate Metastasis to the Liver

Liver metastasis is associated with some of the worst clinical outcomes compared with other sites [32,33]. Out of all the patient with liver metastasis, those which originated from the prostate have the second worse survival (behind testicular cancer) [34]. Kelly et al. (2012) report that patients with liver metastases had a median survival of 14.4 months compared with 22.2 months in patients with non-liver metastases [35]. A meta-analysis of PCa samples in the SEER dataset (n = 10,777) confirmed that the presence of liver metastasis in patients associated with the worst cancer specific and overall survival [36]. A full summary of the effects of visceral metastases on patient outcomes in different patient cohorts is shown in Table 1.

In general, AR status of PCa cells has an inverse correlation with neuroendocrine features (Figure 2B). Publicly available data suggest that AR-negative and neuroendocrine disease are most often found in liver metastases (Figure 2A), indeed anecdotally, liver metastases are usually presumed to all be AR-negative and neuroendocrine. However, a mixture of AR-positive or -negative neuroendocrine phenotypes, or indeed AR-negative non-neuroendocrine PCa, have been seen, with varying degrees of heterogeneity within each tumor [37]. The data also suggest that in PCa, liver metastases can be either composed of AR-negative/neuroendocrine disease or AR-positive/adenocarcinoma disease, and in some cases potentially a mixture of the two types (Figure 2C). Patients with liver metastases have can have high circulating PSA levels, indeed in meta-analysis of multiple studies, relating to 8820 men in total with mCRPC, patients with liver metastasis (n = 752 men) had the highest median levels of serum PSA of all the metastatic sites tested [8].

Compared to other metastatic sites for PCa, liver metastases reportedly have the highest fraction of genomic alterations and there are also potential liver specific alterations such as MYC amplification, PTEN deletion or PIK3CB amplification [33]. PCa may undergo site specific transcriptional changes, whereby the tumors adapt to survive and thrive in that specific micro-environment, and it may be that the changes in metabolism pathways are especially important to PCa that have located to the liver [38,39]. All three of these proteins have been linked with metabolism: PTEN with glycolysis and mitochondrial activity [40], MYC regulates genes involved in biogenesis of ribosomes and mitochondria, and glucose/glutamine metabolism [41], while PIK3CB is associated with metabolism of cholesterol, triglycerides, and sugars [42,43].

In other cancers that invade the liver, measurable changes have been noted in liver function serum markers alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin (TBIL), gamma glutamyltransferase (GGT), alkaline phosphatase (ALP), albumin (ALB), and carcinoembryonic antigen (CEA) [44–46]. Serum markers of liver function are also dysregulated when PCa invades the liver [47]. In an analysis of 1281 men with PCa, increased serum levels of AST and/or LDH, or a decreasing serum hemoglobin, were associated with an increased probability of PCa metastasis to the liver [47].

Liver metastases express the epithelial-characteristic adhesion protein E-cadherin at a level that is equivalent to or higher than matched primary tumors [48–50]. This is different to what is observed at other metastatic sites, where E-cadherin is more often expressed at low levels, and may suggest that tumors that metastasize to the liver have a different relationship to other cell types and the local microenvironment in terms of cell–cell and cell-ECM interaction. The liver microenvironment is considered vastly different to other metastatic sites, such as the bone [51] and it has been postulated that the microenvironment of the liver plays a role in determining the "types" of PCa that will successfully colonize the liver and how lethal they will be [51,52]. In other solid tumors that metastasize to

the liver, proliferating cancer cells in the liver form subclinical micro-metastases in the periportal regions of the liver lobule, and their growth and survival is supported by the host parenchymal and stromal cells [53]. In liver spread of colon, pancreatic, and breast cancers, the presence and activation of resident stellate cells is important in preparing a microenvironment that propagates metastatic seeding [54] and growth [55–58]. The ability of stellate cell activation to influence metastatic growth is reported to involve their ability to influence fibrosis and ECM deposition/stiffness [58–60]. It will be interesting to confirm how the liver microenvironment actually responds to PCa.

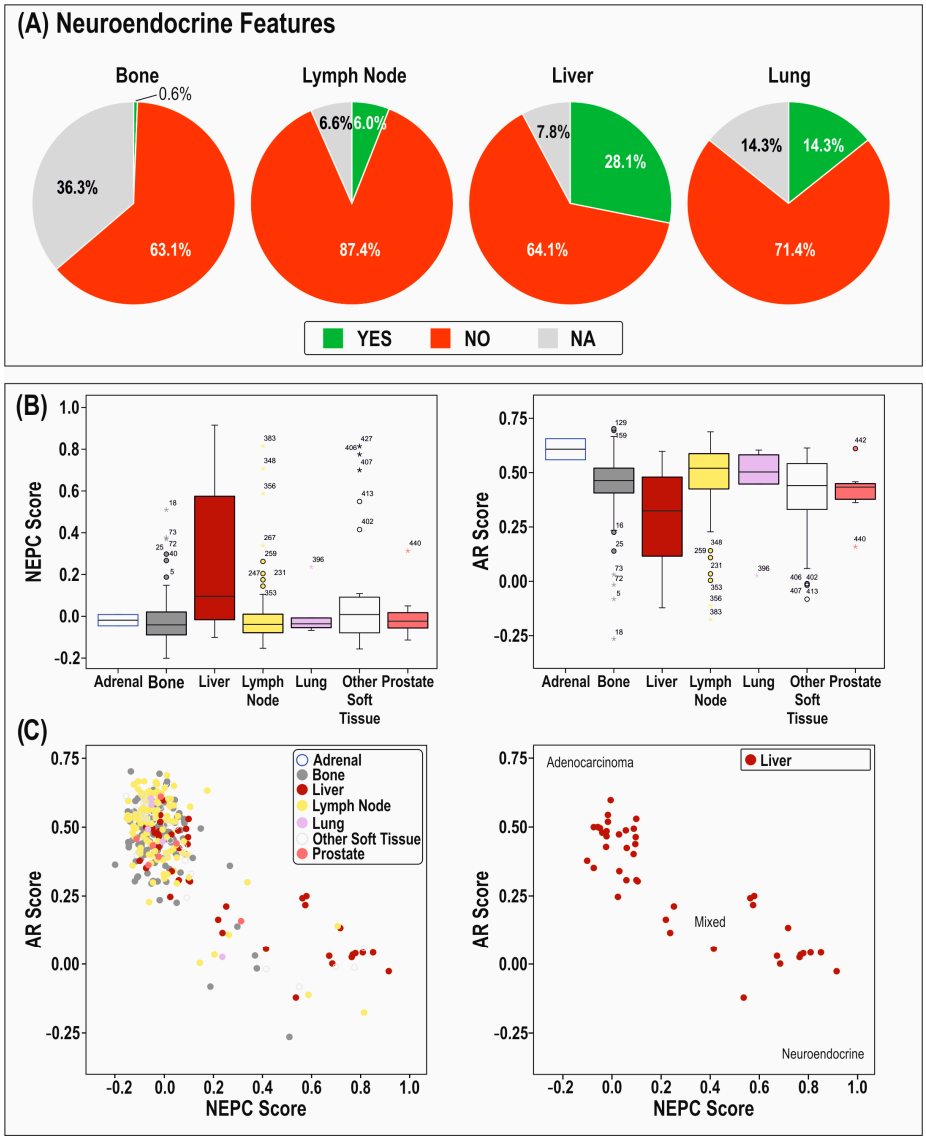

Figure 2. Characteristics of prostate cancer cells in the liver. A summary of data from Stand Up to Cancer (SU2C) database showing the cellular characteristics of prostate cancer cells that have metastasized to the bone (n = 160), lymph node (n = 167), liver (n = 64), and lung (n = 7). (**A**) The percentage of metastatic tumors with pathologist defined neuroendocrine features. Green = metastases with neuroendocrine features, red = no neuroendocrine features, and grey = no characterization available. (**B**) Analysis of (i) neuroendocrine prostate cancer (NEPC) gene scores and (ii) androgen receptor (AR) activity gene scores in different metastatic sites. (**C**) Comparison of NEPC (horizontal) and AR (vertical) gene scores in (i) different metastatic sites, and (ii) the liver alone. Analyzed using publicly available data [61].

4. Anti-Androgens and Patients with Liver Metastases

As stated earlier, PCa growth is dependent on androgens, which are male sex hormones that work through the androgen receptor (AR) [62]. The AR is a nuclear transcription factor activated by testosterone or dihydrotestosterone (DHT) and is a key driver in PCa development and progression [63]. Androgen deprivation therapy (ADT) is common treatment for recurrent or metastatic PCa [64]. These therapies work by either reducing circulating testosterone levels or inhibiting androgen binding to AR; both approaches reduce AR activity [65]. The latest generation of anti-androgens includes enzalutamide, and more recently darolutamide and apalutamide [10,66], and these are generally effective in lowering PSA levels, reducing tumor burden, and increasing patient survival [11,67]. These have varying success rates, dependent on when in the disease progression they are administered and the status, e.g., whether the primary site is intact [10,68].

One of the principal factors that determine the responsiveness and overall success of anti-androgen therapies is the site of metastasis. The poor clinical outcomes associated with visceral metastases, in particular liver metastases [30] (Table 1), could be in part due to the reported unresponsiveness of liver metastases to multiple types of anti-androgen therapy [8,9,69–71]. There have been studies reporting success of anti-androgen therapies in liver metastasis cases [72], however, many suggest this effect is short-lived [9]. A possible explanation for this may be that liver metastasis is considered to be a late event in disease progression, linked to neuroendocrine tumor characteristics including lack of AR expression (see above), and therefore represents an aggressive subset which does not respond well to therapy [69]. However, as discussed, there are cases of AR-expressing adenocarcinoma metastasizing to the liver, which could be responsive. Furthermore, liver metastases can occur in patients who do not exhibit bone metastases, with limited differences in survival between patients with liver only metastasis compared to patients with liver plus other metastatic sites [8,28].

Reports also suggest that cases of liver metastases are increasing and this could possibly be linked to the use of anti-androgen therapies [5,31,73]. This could be due to anti-androgens exerting selecting pressure that favors cancer cells that home to the liver, or selecting for neuro-endocrine type tumors [74]. This may also suggest anti-androgen therapies are having a more significant impact on the liver itself than previously thought—as discussed below, there is evidence for links with fibrosis.

Table 1. Summary of clinical trials to assess efficacy of anti-androgen therapies and response of patients with visceral metastasis.

Paper	# of Patients	Tumor Type	Treatment	Outcome
Conteduca et al., 2015 [75]	265	CRPC	Abiraterone	VM linked to reduced OS
Goodman et al., 2014 [76]	1195	CRPC	Abiraterone acetate or placebo	VM associated with reduced PFS and OS in both groups
Poon et al., 2016 [77]	110	mCRPC	Abiraterone acetate	Chemotherapy naïve-VM reduced OS and PFS Chemotherapy received-VM no sig. dif.
Moschini et al., 2016 [78]	1011	LN + ve PCa		VM had poor OS VM had greater HR
Gandaglia et al., 2015 [79]	3857	mPCa		VM alone or with BM had worse OS and PFS than BM or LN
Conteduca et al., 2016 [80]	193	mCRPC	Enzalutamide	VM increased HR but not significant
Armstrong et al., 2007 [81]	1006	mCRPC	Docetaxel, mitoxantrone, prednisone	VM and multiple sites had higher HR
Pond et al., 2014 [32]	1006	mCRPC	Docetaxel, mitoxantrone, prednisone	Liver or lung had worse OS than BM
Terada et al., 2016 [82]	329	mPCa	Enzalutamide	VM increased CRPC development more than BM, lower PFS than BM or LN
Shiota et al., 2014 [83]	97	CRPC	Docetaxel and Prednisone	VM has worse OS and PFS
Loriot et al., 2013 [84]	307	mCRPC	Enzalutamide (previous docetaxel)	OS increased in lung and liver, bigger effect in lung
Loriot et al., 2017 [85]	1199	CRPC	Enzalutamide	OS increased in lung and liver, bigger effect in lung
Penson et al., 2016 [86]	396	CRPC	Enzalutamide vs. Bicalutamide	Enzalutamide had better PFS
Davies et al., 2019 [87]	1125	mPCa	Testosterone and Enzalutamide	Better OS and PFS with testosterone/enza vs. control
Eisenberger et al., 1998 [88]	1378	mPCa	Flutamide	No sig. dif. in OS

CRPC = castration resistant prostate cancer, mCRPC = metastatic castrate resistant prostate cancer, LN + PCa = lymph node positive prostate cancer, mPCa = metastatic prostate cancer, LHRH = luteinizing hormone-releasing hormone, VM = visceral metastasis, PFS = progression free survival, OS = overall survival, BM = bone metastasis, HR = 5-year hazard ratio, Enza = Enzalutamide.

5. The Influence of Microenvironment on PCa Progression and Its Relationship with AR

The influence of the microenvironment is seen throughout all stages of cancer development and progression and therefore, therapies to target cancers must consider the effect of (and on) the tumor microenvironment.

Prostate development is reliant on the interactions between epithelial cells and the surrounding stroma in the microenvironment. The prostatic stroma is composed of several non-malignant cell types such as fibroblasts, smooth muscle cells, endothelial cells and immune cells [89]. In cancer, the components of the stroma also undergo a type of transformational change and the signaling between cancer cells and the microenvironment is altered [90]. In the primary site, the prostate microenvironment changes from the benign context of smooth muscle cells and fibroblasts, to the cancer-associated microen-

vironment largely composed of fibroblasts with an activated phenotype, termed cancer associated fibroblasts (CAFs) [91]. CAFs are spindle-shaped cells that are derived from the fibroblasts present in the normal microenvironment [23,25,92], but differ from them by producing elevated levels of collagen and ECM proteins and upregulating the secretion of pro-tumorigenic factors [93] to facilitate tumor growth, invasion and metastasis [94]. In addition, this CAF microenvironment secretes growth factors which promote angiogenesis, alter ECM architecture, and accelerates fibroblast proliferation [95]. Without these changes to the microenvironment, cancer cells cannot invade and metastasize.

Androgen receptors are not just expressed in cancerous epithelial cells, but in multiple cell types of the prostate stroma [89,96]. Stromal AR is well documented to be essential for normal prostate growth and development [97]. In PCa, reduced AR levels in the stroma is frequently associated with poor clinical outcomes [24,98–103]. Moreover, low stromal AR expression is linked to tumor resistance to ADT [103] and relapse in PCa patients [100]. This is the opposite of AR's effect in epithelial cells, where high levels of AR were found to be associated with a more aggressive disease phenotype [24]. A meta-analysis of protein markers in PCa confirmed that low or no AR expression in the PCa stroma associated with worse patient outcomes, and stromal AR is in fact one of the only markers that consistently associates with progression [104,105]. Niu et al. (2008) also suggest stromal AR is essential for cancer initiation and growth in mouse xenograft models using WPMY cells, with reduced AR in the stroma found to be effective at reducing tumor growth initially; they then also suggest low stromal AR suppressed metastasis [106], although these cell line data are not supported with clinical findings. This may suggest the effect of AR expression is dependent on the stage and progression of the disease, and AR may play a different role as the disease changes. Given the significance of AR in stroma of the primary site, the effect of anti-androgens on the metastatic microenvironment warrants further consideration.

The role of AR in the metastatic microenvironments is generally under-investigated, this is particularly true for the liver. A number of articles have suggested that the liver is responsive to androgens and expresses AR both in the nucleus and cytoplasm (only determined in whole tissue extracts and hepatocytes) [107–111]. Single cell RNA-sequencing data sets show detectable AR RNA heterogeneously expressed throughout the liver, but mainly in hepatocytes, vasculature and mesenchymal cells (fibroblasts/stellate cells) although there are also a few immune cell types which express AR (Figure 3).

There is some data suggesting an association between hepatic AR and reduced immune infiltration [112] and enabling glycolysis and metabolism [113]. Additionally, androgens may have a role in regulating the secretion of cytokines and growth factors, such as TGF-ß and VEGF, by hepatocytes [113,114]. Importantly, TGF-ß is integral to fibrotic responses, and is also known to be increased in PCa liver metastases [51,115], and to promote invasion and metastasis, all potential reasons why cancer cells metastasize to and grow in the liver [116]. CAFs, detectable in prostate liver metastases [117], potentially work in combination with host mesenchymal cells (stellate cells), which are recruited intra-metastatically and incorporated to form a stroma which releases growth factors and ECM proteins to support cancer cell growth [53]. It is not yet known whether AR signaling in these two cell types will resemble what we have previously reported for AR in prostatic fibroblasts [24,25]. Despite this emerging research, the role of androgen signaling in the liver metastatic microenvironment and its involvement in influencing local cancer cell biology is not well defined.

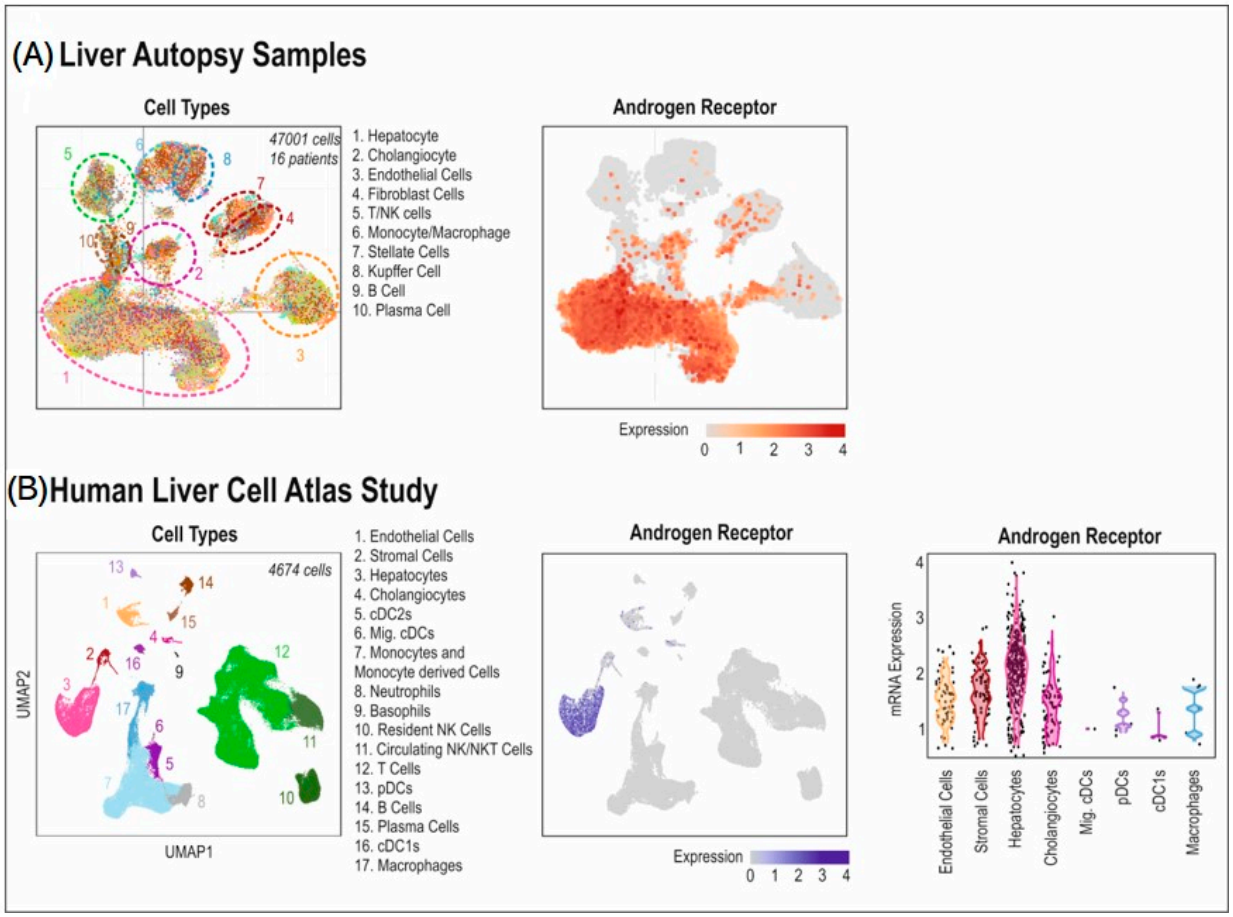

Figure 3. AR expression in the cells of the liver. Single cell RNA-seq analysis of human liver from two different studies. (**A**) Liver autopsy samples [118] of 47,001 cells in total from 16 patients. (i) UMAP graph of single cells collected from different patients' livers. Each sample is colored by which patient they come from, and surrounded by a dotted line indicating which cell types compose each group. (ii) Analysis of AR expression in each single cell, with expression scaled from grey (no expression) to increasing shades of red (increasing levels of AR expression). (**B**) The Human Liver Cell Atlas Study (GSE192742 [119]), comprised of 4647 cells from human liver. (i) UMAP graph showing the cell-types present in this sample. (ii) Analysis of AR expression in each single cell, with expression scaled from grey (no expression) and deepening shades of blue (increasing levels of AR expression). (iii) Violin plots of AR expression in a sub-set of the cell-types detected in the study.

6. How the Liver Responds to Anti-Androgen Therapies

It is underappreciated that all cell types throughout the body express some form of nuclear/sex hormone receptor [120]. Cell comprising the liver express all steroid receptors, including AR, and the liver appears to be an androgen responsive organ [121,122], which may be further suggested by the gender imbalance in all types of liver disease and fibrotic states [108,121,123–125]. In a study of 117 men, higher levels of testosterone were associated with lower serum ALT and AST [126]. There have been suggestions that androgen metabolism and liver cirrhosis are linked [127]. Indeed androgen (and estrogen) levels have been associated with development of liver disease [128]. Furthermore, prohibitin (PHB), an AR co-repressor protein [129–131], is associated with liver injury and cancer [132], and importantly in a liver specific PHB knock out mouse model, there was upregulation of genes involved in fibrosis [133]. Sex also appears to influence the incidence of liver metastasis, with men twice as likely to present with liver metastases than women [134]. Interestingly in a mouse model of diethylnitrosamine (a hepatotoxicant and hepatocarcinogen)-induced formation of hepatocellular carcinoma (HCC), this treatment was also associated with fibro-

sis and accumulation of AR positive mesenchymal cells and immune cells [112]. This may support the previously mentioned hypothesized link between AR and fibrotic responses in the liver.

Liver injury associated with anti-androgen therapies has been reported in the literature since as early as the 1940s [135]. Analysis of the SEER database indicated that in men receiving some form of ADT, there was a significant association with subsequent diagnosis of liver disease, including non-alcoholic fatty liver disease, cirrhosis and necrosis [136]. Liver injury was associated with anti-androgen therapies involving first-generation antiandrogens such as Flutamide, albeit rarely [14]. The same report also identified a case of liver toxicity associated with Nilutamide administration. Yun et al. (2016) also reported liver injury associated with (second generation antiandrogen) bicalutamide treatment [137], with histology demonstrating acute intrahepatic cholestasis suggestive that the injury was caused by anti-androgen administration. In large trials assessing the use of abiraterone, which is a steroid synthesis inhibitor that has also been shown to have antiandrogen effects [138], there have been trends of liver enzyme increases indicative of damage/reduced function. In a PCa cohort of 1917 patients, the administration of abiraterone saw the percentage of patients with increased ALT and AST levels rise from below 1% to 6% (53 patients) [139]. In the COU-AA trial of prednisone alone or in combination with abiraterone, there was a small increase in abnormal liver function tests, with the number of patients with increased AST and ALT doubling from, respectively, 5% and 4.8% of patients with prednisone alone to 13.3% and 12% in patients with prednisone and abiraterone, albeit this involved a small number of patients and the effect was not quite significant [140,141]. This trend was observed in other trials involving abiraterone combinations, where small increases in the number of patients with high levels of LDH, AST and ALT were observed [12,142]. The increase in liver enzymes can resolve with time [143], but the effect of this increase and potential damage to the liver is unknown. So, whilst not all patients will have liver damage events in response to anti-androgens, it may be worthwhile monitoring those patients that do for subsequent metastases.

7. Potential for the Formation of a Pre-Metastatic Niche

A major concern of tissue response to injury is the possible formation of a pre-metastatic niche. A pre-metastatic niche is a microenvironment which is suitable/optimal for colonization by circulating tumor cells [144]—the "soil" in the 'seed and soil' hypothesis [145,146]. In the liver, changes to the stromal cells and ECM in response to liver injury produce an environment conducive for cancer cell seeding [146] and patients with liver fibrosis have an increased risk of developing liver cancer [147]. Liver injury and fibrosis have also been associated with subsequent metastases, with the fibrotic environment providing a niche for cancer growth [18,19,148,149]. Liver injury creating a pre-metastatic niche has been reported in pancreatic and colorectal cancer [18–20,150,151].

The fibrosis/wound healing activated in response to injury in the liver is similar to the changes observed in the microenvironment of cancer metastases discussed earlier (Figure 1). Hepatic stellate cells are essential for the liver's response to injury, becoming activated and transforming into myofibroblast-like cells which produce ECM, culminating in wound healing responses to protect the liver, but simultaneously reducing tissue structure and function [152]. There is also an accrual of fibroblasts, which also aid ECM production and accumulation [153]. The TGF-ß and ECM produced by activated stellate cells has been reported to increase cancer invasion and proliferation in pancreatic and colon models, while activation of stellate cells is reported to activate growth of dormant breast cancer micrometastases [154]. In colorectal cancer, patients with a fibrotic liver had a four-fold increased risk of liver metastasis compared to those with a normal liver [19]. In terms of mechanisms involved, we may gain insight from other metastatic sites. For example, in lung metastasis, cases have been shown to be more severe where increased fibronectin and stiffening of the ECM are present, which can nurture growth by overriding tumor suppressor activity [155]. Fibronectin produced by activated stellate cells has been reported to cause recruitment

of bone marrow-derived immune cells, creating an environment that allowed metastatic growth of pancreatic cancer cells in animal models [156]. Activated stellate cells have also been reported to secrete CCL20 and increase fibronectin deposition, promoting colorectal cancer cell line metastasis to the liver in mouse models [54]. Colorectal metastasis has also been reported to be enhanced by tenascin C produced by activated stellate cells [157]. Activation of stellate cells has been reported to alter the ECM they produce, increasing collagen and periostin, to promote metastatic growth of pancreatic cells [158]. Alterations in ECM components activate intracellular signaling pathways, such as the Akt pathway, in cancer cells to promote invasion, seeding, growth, and survival [159]. Importantly, it should be noted that the ECM is able to affect the sensitivity/responsiveness of cancer cells to therapy [160]. In a meta-analysis of five PCa studies (434 samples), genes involved in focal adhesion signaling were significantly altered in liver metastases [38], indicating that cell-ECM adhesion/interactions have an important role in cancer metastases. Additionally, the activation of stellate cells also causes the secretion of a milieu of growth factors and cytokines (PDGFs, HGF, TGF-β, SDF-1, VEGF, PGF, FGFs, CXCLs) which can also promote cancer proliferation and development of micro-metastases [161].

Given the responsiveness of the liver to androgens, there is potential that anti-androgen therapies may contribute to reported liver injury associated with administration. A worrying potential result of this side-effect may be the creation of a microenvironment more hospitable to metastatic seeding and growth in certain patients.

8. Conclusions

Metastasis to the liver has one of the worst cancer outcomes yet there is relatively little known about liver metastases, the role of the liver microenvironment, and why prognosis is so poor. It is important to investigate these aspects of the disease given the reported increase in cases. Current treatment options, including anti-androgen therapies, have limited success rates in liver metastasis cases. When comparing the effectiveness of anti-androgen therapies, patient with liver metastases were significantly less responsive than patients with only bone metastases [8,31]. In some patients, anti-androgen therapy (perhaps particularly flutamide and bicalutamide) can induce liver injury [14,137]. In response, the liver recruits cells to form scar tissue—a similar response to what is observed in the formation of a pre-metastatic niche. A concern is this side effect may result in the area becoming more attractive to cancer cell invasion [146]. This may need to become a research priority to ensure treatment does not result in disease progression to a lethal stage. The changes seen to the liver microenvironment are poorly characterized; further research is required to determine why prostate cancer often spreads here and why such poor clinical outcomes are associated with liver metastasis.

Author Contributions: Conceptualization, D.A.L. and C.L.B.; writing, A.K.B., S.A. and D.A.L.; review and editing, D.A.L. and C.L.B. All authors have read and agreed to the published version of the manuscript.

Funding: The authors are grateful for support during writing of this review from the NIHR Imperial Biomedical Research Centre (BRC), Prostate Cancer Foundation (PCF) (Young Investigator Award to DAL), and Prostate Cancer UK (PCUK) (RIA18-ST2-022).

Acknowledgments: The views expressed are those of the author (s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J. Clin.* **2021**, *71*, 209–249. [CrossRef] [PubMed]
2. Wang, H.; Li, B.; Zhang, P.; Yao, Y.; Chang, J. Clinical characteristics and prognostic factors of prostate cancer with liver metastases. *Tumour Biol.* **2014**, *35*, 595–601. [CrossRef] [PubMed]

3. Beer, T.M.; Tombal, B. Enzalutamide in metastatic prostate cancer before chemotherapy. *N. Engl. J. Med.* **2014**, *371*, 1755–1756. [CrossRef] [PubMed]
4. Lawson, D.A.; Zong, Y.; Memarzadeh, S.; Xin, L.; Huang, J.; Witte, O.N. Basal epithelial stem cells are efficient targets for prostate cancer initiation. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 2610–2615. [CrossRef]
5. Doctor, S.M.; Tsao, C.K.; Godbold, J.H.; Galsky, M.D.; Oh, W.K. Is prostate cancer changing?: Evolving patterns of metastatic castration-resistant prostate cancer. *Cancer* **2014**, *120*, 833–839. [CrossRef]
6. Tsilimigras, D.I.; Brodt, P.; Clavien, P.A.; Muschel, R.J.; D'Angelica, M.I.; Endo, I.; Parks, R.W.; Doyle, M.; de Santibanes, E.; Pawlik, T.M. Liver metastases. *Nat. Rev. Dis. Primers* **2021**, *7*, 27. [CrossRef]
7. Liu, L.X.; Zhang, W.H.; Jiang, H.C. Current treatment for liver metastases from colorectal cancer. *World J. Gastroenterol.* **2003**, *9*, 193–200. [CrossRef]
8. Halabi, S.; Kelly, W.K.; Ma, H.; Zhou, H.; Solomon, N.C.; Fizazi, K.; Tangen, C.M.; Rosenthal, M.; Petrylak, D.P.; Hussain, M.; et al. Meta-Analysis Evaluating the Impact of Site of Metastasis on Overall Survival in Men with Castration-Resistant Prostate Cancer. *J. Clin. Oncol.* **2016**, *34*, 1652–1659. [CrossRef]
9. Singh, A.; Cheedella, N.K.S.; Shakil, S.A.; Gulmi, F.; Kim, D.S.; Wang, J.C. Liver Metastases in Prostate Carcinoma Represent a Relatively Aggressive Subtype Refractory to Hormonal Therapy and Short-Duration Response to Docetaxel Monotherapy. *World J. Oncol.* **2015**, *6*, 265–269. [CrossRef]
10. Estebanez-Perpina, E.; Bevan, C.L.; McEwan, I.J. Eighty Years of Targeting Androgen Receptor Activity in Prostate Cancer: The Fight Goes on. *Cancers* **2021**, *13*, 509. [CrossRef]
11. Bohl, C.E.; Gao, W.; Miller, D.D.; Bell, C.E.; Dalton, J.T. Structural basis for antagonism and resistance of bicalutamide in prostate cancer. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 6201–6206. [CrossRef] [PubMed]
12. Fizazi, K.; Shore, N.; Tammela, T.L.; Ulys, A.; Vjaters, E.; Polyakov, S.; Jievaltas, M.; Luz, M.; Alekseev, B.; Kuss, I.; et al. Darolutamide in Nonmetastatic, Castration-Resistant Prostate Cancer. *N. Engl. J. Med.* **2019**, *380*, 1235–1246. [CrossRef] [PubMed]
13. Sinclair, M.; Grossmann, M.; Gow, P.J.; Angus, P.W. Testosterone in men with advanced liver disease: Abnormalities and implications. *J. Gastroenterol. Hepatol.* **2015**, *30*, 244–251. [CrossRef] [PubMed]
14. Gomez, J.L.; Dupont, A.; Cusan, L.; Tremblay, M.; Suburu, R.; Lemay, M.; Labrie, F. Incidence of liver toxicity associated with the use of flutamide in prostate cancer patients. *Am. J. Med.* **1992**, *92*, 465–470. [CrossRef] [PubMed]
15. Wang, S.; Friedman, S.L. Hepatic fibrosis: A convergent response to liver injury that is reversible. *J. Hepatol.* **2020**, *73*, 210–211. [CrossRef] [PubMed]
16. Williamson, T.; Sultanpuram, N.; Sendi, H. The role of liver microenvironment in hepatic metastasis. *Clin. Transl. Med.* **2019**, *8*, 21. [CrossRef]
17. Hudson, S.V.; Miller, H.A.; Mahlbacher, G.E.; Saforo, D.; Beverly, L.J.; Arteel, G.E.; Frieboes, H.B. Computational/experimental evaluation of liver metastasis post hepatic injury: Interactions with macrophages and transitional ECM. *Sci. Rep.* **2019**, *9*, 15077. [CrossRef]
18. Hu, X.; Marietta, A.; Dai, W.X.; Li, Y.Q.; Ma, X.J.; Zhang, L.; Cai, S.J.; Peng, J.J. Prediction of hepatic metastasis and relapse in colorectal cancers based on concordance analyses with liver fibrosis scores. *Clin. Transl. Med.* **2020**, *9*, 13. [CrossRef]
19. Kondo, T.; Okabayashi, K.; Hasegawa, H.; Tsuruta, M.; Shigeta, K.; Kitagawa, Y. The impact of hepatic fibrosis on the incidence of liver metastasis from colorectal cancer. *Br. J. Cancer* **2016**, *115*, 34–39. [CrossRef]
20. Lee, J.W.; Stone, M.L.; Porrett, P.M.; Thomas, S.K.; Komar, C.A.; Li, J.H.; Delman, D.; Graham, K.; Gladney, W.L.; Hua, X.; et al. Hepatocytes direct the formation of a pro-metastatic niche in the liver. *Nature* **2019**, *567*, 249–252. [CrossRef]
21. Del Rio, M.; Mollevi, C.; Vezzio-Vie, N.; Bibeau, F.; Ychou, M.; Martineau, P. Specific extracellular matrix remodeling signature of colon hepatic metastases. *PLoS ONE* **2013**, *8*, e74599. [CrossRef] [PubMed]
22. Palumbo, A., Jr.; Ferreira, L.B.; Reis de Souza, P.A.; Oliveira, F.L.; Pontes, B.; Viana, N.B.; Machado, D.E.; Palmero, C.Y.; Alves, L.M.; Gimba, E.R.; et al. Extracellular matrix secreted by reactive stroma is a main inducer of pro-tumorigenic features on LNCaP prostate cancer cells. *Cancer Lett.* **2012**, *321*, 55–64. [CrossRef] [PubMed]
23. Barron, D.A.; Rowley, D.R. The reactive stroma microenvironment and prostate cancer progression. *Endocr.-Relat. Cancer* **2012**, *19*, R187–R204. [CrossRef] [PubMed]
24. Leach, D.A.; Need, E.F.; Toivanen, R.; Trotta, A.P.; Palenthorpe, H.M.; Tamblyn, D.J.; Kopsaftis, T.; England, G.M.; Smith, E.; Drew, P.A.; et al. Stromal androgen receptor regulates the composition of the microenvironment to influence prostate cancer outcome. *Oncotarget* **2015**, *6*, 16135–16150. [CrossRef] [PubMed]
25. Leach, D.A.; Buchanan, G. Stromal Androgen Receptor in Prostate Cancer Development and Progression. *Cancers* **2017**, *9*, 10. [CrossRef]
26. Cunha, G.R.; Lung, B. The possible influence of temporal factors in androgenic responsiveness of urogenital tissue recombinants from wild-type and androgen-insensitive (Tfm) mice. *J. Exp. Zool.* **1978**, *205*, 181–193. [CrossRef]
27. Donjacour, A.A.; Cunha, G.R. Assessment of prostatic protein secretion in tissue recombinants made of urogenital sinus mesenchyme and urothelium from normal or androgen-insensitive mice. *Endocrinology* **1993**, *132*, 2342–2350. [CrossRef]
28. Gandaglia, G.; Abdollah, F.; Schiffmann, J.; Trudeau, V.; Shariat, S.F.; Kim, S.P.; Perrotte, P.; Montorsi, F.; Briganti, A.; Trinh, Q.D.; et al. Distribution of metastatic sites in patients with prostate cancer: A population-based analysis. *Prostate* **2014**, *74*, 210–216. [CrossRef]

29. Shou, J.; Zhang, Q.; Wang, S.; Zhang, D. The prognosis of different distant metastases pattern in prostate cancer: A population based retrospective study. *Prostate* **2018**, *78*, 491–497. [CrossRef]
30. Alumkal, J.J.; Chowdhury, S.; Loriot, Y.; Sternberg, C.N.; de Bono, J.S.; Tombal, B.; Carles, J.; Flaig, T.W.; Dorff, T.B.; Phung, D.; et al. Effect of Visceral Disease Site on Outcomes in Patients with Metastatic Castration-resistant Prostate Cancer Treated with Enzalutamide in the PREVAIL Trial. *Clin. Genitourin Cancer* **2017**, *15*, 610–617.e613. [CrossRef]
31. Pezaro, C.; Omlin, A.; Lorente, D.; Rodrigues, D.N.; Ferraldeschi, R.; Bianchini, D.; Mukherji, D.; Riisnaes, R.; Altavilla, A.; Crespo, M.; et al. Visceral disease in castration-resistant prostate cancer. *Eur. Urol.* **2014**, *65*, 270–273. [CrossRef] [PubMed]
32. Pond, G.R.; Sonpavde, G.; de Wit, R.; Eisenberger, M.A.; Tannock, I.F.; Armstrong, A.J. The prognostic importance of metastatic site in men with metastatic castration-resistant prostate cancer. *Eur. Urol.* **2014**, *65*, 3–6. [CrossRef] [PubMed]
33. Alshalalfa, M.; Seldon, C.; Franco, I.; Vince, R.; Carmona, R.; Punnen, S.; Kaochar, S.; Dess, R.; Kishan, A.; Spratt, D.E.; et al. Clinicogenomic characterization of prostate cancer liver metastases. *Prostate Cancer Prostatic Dis.* **2022**, *25*, 366–369. [CrossRef] [PubMed]
34. Horn, S.R.; Stoltzfus, K.C.; Lehrer, E.J.; Dawson, L.A.; Tchelebi, L.; Gusani, N.J.; Sharma, N.K.; Chen, H.; Trifiletti, D.M.; Zaorsky, N.G. Epidemiology of liver metastases. *Cancer Epidemiol.* **2020**, *67*, 101760. [CrossRef] [PubMed]
35. Kelly, W.K.; Halabi, S.; Carducci, M.; George, D.; Mahoney, J.F.; Stadler, W.M.; Morris, M.; Kantoff, P.; Monk, J.P.; Kaplan, E.; et al. Randomized, double-blind, placebo-controlled phase III trial comparing docetaxel and prednisone with or without bevacizumab in men with metastatic castration-resistant prostate cancer: CALGB 90401. *J. Clin. Oncol.* **2012**, *30*, 1534–1540. [CrossRef]
36. Deng, Y.; Bi, R.; Zhu, Z.; Li, S.; Xu, B.; Rather, W.A.; Wang, C. A Surveillance, Epidemiology and End Results database analysis of the prognostic value of organ-specific metastases in patients with advanced prostatic adenocarcinoma. *Oncol. Lett.* **2019**, *18*, 1057–1070. [CrossRef]
37. Brady, L.; Kriner, M.; Coleman, I.; Morrissey, C.; Roudier, M.; True, L.D.; Gulati, R.; Plymate, S.R.; Zhou, Z.; Birditt, B.; et al. Inter- and intra-tumor heterogeneity of metastatic prostate cancer determined by digital spatial gene expression profiling. *Nat. Commun.* **2021**, *12*, 1426. [CrossRef]
38. Samarzija, I. Site-Specific and Common Prostate Cancer Metastasis Genes as Suggested by Meta-Analysis of Gene Expression Data. *Life* **2021**, *11*, 636. [CrossRef]
39. Hartung, F.; Patil, A.; Meshram, R.J.; Weber, G.F. Gene expression signatures of site-specificity in cancer metastases. *Clin. Exp. Metastasis* **2020**, *37*, 159–171. [CrossRef]
40. Chen, C.Y.; Chen, J.; He, L.; Stiles, B.L. PTEN: Tumor Suppressor and Metabolic Regulator. *Front. Endocrinol.* **2018**, *9*, 338. [CrossRef]
41. Dang, C.V.; Le, A.; Gao, P. MYC-induced cancer cell energy metabolism and therapeutic opportunities. *Clin. Cancer Res.* **2009**, *15*, 6479–6483. [CrossRef] [PubMed]
42. Jia, S.; Liu, Z.; Zhang, S.; Liu, P.; Zhang, L.; Lee, S.H.; Zhang, J.; Signoretti, S.; Loda, M.; Roberts, T.M.; et al. Essential roles of PI(3)K-p110beta in cell growth, metabolism and tumorigenesis. *Nature* **2008**, *454*, 776–779. [CrossRef] [PubMed]
43. Ciraolo, E.; Iezzi, M.; Marone, R.; Marengo, S.; Curcio, C.; Costa, C.; Azzolino, O.; Gonella, C.; Rubinetto, C.; Wu, H.; et al. Phosphoinositide 3-kinase p110beta activity: Key role in metabolism and mammary gland cancer but not development. *Sci. Signal.* **2008**, *1*, ra3. [CrossRef] [PubMed]
44. Wu, X.Z.; Ma, F.; Wang, X.L. Serological diagnostic factors for liver metastasis in patients with colorectal cancer. *World J. Gastroenterol.* **2010**, *16*, 4084–4088. [CrossRef] [PubMed]
45. He, M.M.; Fang, Z.; Hang, D.; Wang, F.; Polychronidis, G.; Wang, L.; Lo, C.H.; Wang, K.; Zhong, R.; Knudsen, M.D.; et al. Circulating liver function markers and colorectal cancer risk: A prospective cohort study in the UK Biobank. *Int. J. Cancer* **2021**, *148*, 1867–1878. [CrossRef] [PubMed]
46. Cao, R.; Wang, L.P. Serological diagnosis of liver metastasis in patients with breast cancer. *Cancer Biol. Med.* **2012**, *9*, 57–62. [CrossRef]
47. Cotogno, P.M.; Ranasinghe, L.K.; Ledet, E.M.; Lewis, B.E.; Sartor, O. Laboratory-Based Biomarkers and Liver Metastases in Metastatic Castration-Resistant Prostate Cancer. *Oncologist* **2018**, *23*, 791–797. [CrossRef]
48. Chao, Y.; Wu, Q.; Acquafondata, M.; Dhir, R.; Wells, A. Partial mesenchymal to epithelial reverting transition in breast and prostate cancer metastases. *Cancer Microenviron.* **2012**, *5*, 19–28. [CrossRef]
49. Ma, B.; Wheeler, S.E.; Clark, A.M.; Whaley, D.L.; Yang, M.; Wells, A. Liver protects metastatic prostate cancer from induced death by activating E-cadherin signaling. *Hepatology* **2016**, *64*, 1725–1742. [CrossRef]
50. Ma, B.; Wells, A.; Wei, L.; Zheng, J. Prostate cancer liver metastasis: Dormancy and resistance to therapy. *Semin. Cancer Biol.* **2021**, *71*, 2–9. [CrossRef]
51. Drake, C.G. Visceral metastases and prostate cancer treatment: 'die hard,' 'tough neighborhoods,' or 'evil humors'? *Oncology* **2014**, *28*, 974–980. [PubMed]
52. Akfirat, C.; Zhang, X.; Ventura, A.; Berel, D.; Colangelo, M.E.; Miranti, C.K.; Krajewska, M.; Reed, J.C.; Higano, C.S.; True, L.D.; et al. Tumour cell survival mechanisms in lethal metastatic prostate cancer differ between bone and soft tissue metastases. *J. Pathol.* **2013**, *230*, 291–297. [CrossRef] [PubMed]
53. Luzzi, K.J.; MacDonald, I.C.; Schmidt, E.E.; Kerkvliet, N.; Morris, V.L.; Chambers, A.F.; Groom, A.C. Multistep nature of metastatic inefficiency: Dormancy of solitary cells after successful extravasation and limited survival of early micrometastases. *Am. J. Pathol.* **1998**, *153*, 865–873. [CrossRef] [PubMed]

54. Zhao, S.; Mi, Y.; Zheng, B.; Wei, P.; Gu, Y.; Zhang, Z.; Xu, Y.; Cai, S.; Li, X.; Li, D. Highly-metastatic colorectal cancer cell released miR-181a-5p-rich extracellular vesicles promote liver metastasis by activating hepatic stellate cells and remodelling the tumour microenvironment. *J. Extracell. Vesicles* **2022**, *11*, e12186. [CrossRef] [PubMed]
55. Correia, A.L.; Guimaraes, J.C.; Auf der Maur, P.; De Silva, D.; Trefny, M.P.; Okamoto, R.; Bruno, S.; Schmidt, A.; Mertz, K.; Volkmann, K.; et al. Hepatic stellate cells suppress NK cell-sustained breast cancer dormancy. *Nature* **2021**, *594*, 566–571. [CrossRef]
56. Dou, C.; Liu, Z.; Tu, K.; Zhang, H.; Chen, C.; Yaqoob, U.; Wang, Y.; Wen, J.; van Deursen, J.; Sicard, D.; et al. P300 Acetyltransferase Mediates Stiffness-Induced Activation of Hepatic Stellate Cells into Tumor-Promoting Myofibroblasts. *Gastroenterology* **2018**, *154*, 2209–2221.e2214. [CrossRef]
57. Herrero, A.; Benedicto, A.; Romayor, I.; Olaso, E.; Arteta, B. Inhibition of COX-2 Impairs Colon Cancer Liver Metastasis through Reduced Stromal Cell Reaction. *Biomol. Ther.* **2021**, *29*, 342–351. [CrossRef]
58. Brodt, P. Role of the Microenvironment in Liver Metastasis: From Pre- to Prometastatic Niches. *Clin. Cancer Res.* **2016**, *22*, 5971–5982. [CrossRef]
59. Lee, C.; Kim, M.; Han, J.; Yoon, M.; Jung, Y. Mesenchymal Stem Cells Influence Activation of Hepatic Stellate Cells, and Constitute a Promising Therapy for Liver Fibrosis. *Biomedicines* **2021**, *9*, 1598. [CrossRef]
60. Liu, Z.; Mo, H.; Liu, R.; Niu, Y.; Chen, T.; Xu, Q.; Tu, K.; Yang, N. Matrix stiffness modulates hepatic stellate cell activation into tumor-promoting myofibroblasts via E2F3-dependent signaling and regulates malignant progression. *Cell Death Dis.* **2021**, *12*, 1134. [CrossRef]
61. Abida, W.; Cyrta, J.; Heller, G.; Prandi, D.; Armenia, J.; Coleman, I.; Cieslik, M.; Benelli, M.; Robinson, D.; Van Allen, E.M.; et al. Genomic correlates of clinical outcome in advanced prostate cancer. *Proc. Natl. Acad. Sci. USA* **2019**, *116*, 11428–11436. [CrossRef] [PubMed]
62. MacLean, H.E.; Chu, S.; Warne, G.L.; Zajac, J.D. Related individuals with different androgen receptor gene deletions. *J. Clin. Investig.* **1993**, *91*, 1123–1128. [CrossRef] [PubMed]
63. Chang, C.; Saltzman, A.; Yeh, S.; Young, W.; Keller, E.; Lee, H.J.; Wang, C.; Mizokami, A. Androgen receptor: An overview. *Crit. Rev. Eukaryot. Gene Expr.* **1995**, *5*, 97–125. [CrossRef] [PubMed]
64. Student, S.; Hejmo, T.; Poterala-Hejmo, A.; Lesniak, A.; Buldak, R. Anti-androgen hormonal therapy for cancer and other diseases. *Eur. J. Pharmacol.* **2020**, *866*, 172783. [CrossRef]
65. Scher, H.I.; Fizazi, K.; Saad, F.; Taplin, M.E.; Sternberg, C.N.; Miller, K.; de Wit, R.; Mulders, P.; Chi, K.N.; Shore, N.D.; et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N. Engl. J. Med.* **2012**, *367*, 1187–1197. [CrossRef]
66. Chen, Y.; Clegg, N.J.; Scher, H.I. Anti-androgens and androgen-depleting therapies in prostate cancer: New agents for an established target. *Lancet Oncol.* **2009**, *10*, 981–991. [CrossRef]
67. Schellhammer, P.F.; Venner, P.; Haas, G.P.; Small, E.J.; Nieh, P.T.; Seabaugh, D.R.; Patterson, A.L.; Klein, E.; Wajsman, Z.; Furr, B.; et al. Prostate specific antigen decreases after withdrawal of antiandrogen therapy with bicalutamide or flutamide in patients receiving combined androgen blockade. *J. Urol.* **1997**, *157*, 1731–1735. [CrossRef]
68. Labrie, F.; Dupont, A.; Belanger, A.; Giguere, M.; Lacoursiere, Y.; Emond, J.; Monfette, G.; Bergeron, V. Combination therapy with flutamide and castration (LHRH agonist or orchiectomy) in advanced prostate cancer: A marked improvement in response and survival. *J. Steroid. Biochem.* **1985**, *23*, 833–841. [CrossRef]
69. Pouessel, D.; Gallet, B.; Bibeau, F.; Avances, C.; Iborra, F.; Senesse, P.; Culine, S. Liver metastases in prostate carcinoma: Clinical characteristics and outcome. *BJU Int.* **2007**, *99*, 807–811. [CrossRef]
70. Armstrong, A.J.; Szmulewitz, R.Z.; Petrylak, D.P.; Holzbeierlein, J.; Villers, A.; Azad, A.; Alcaraz, A.; Alekseev, B.; Iguchi, T.; Shore, N.D.; et al. ARCHES: A Randomized, Phase III Study of Androgen Deprivation Therapy with Enzalutamide or Placebo in Men with Metastatic Hormone-Sensitive Prostate Cancer. *J. Clin. Oncol.* **2019**, *37*, 2974–2986. [CrossRef]
71. Davis, I.D.; Martin, A.J.; Stockler, M.R.; Begbie, S.; Chi, K.N.; Chowdhury, S.; Coskinas, X.; Frydenberg, M.; Hague, W.E.; Horvath, L.G.; et al. Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer. *N. Engl. J. Med.* **2019**, *381*, 121–131. [CrossRef] [PubMed]
72. Rodriguez-Vida, A.; Galazi, M.; Rudman, S.; Chowdhury, S.; Sternberg, C.N. Enzalutamide for the treatment of metastatic castration-resistant prostate cancer. *Drug Des. Dev. Ther.* **2015**, *9*, 3325–3339. [CrossRef] [PubMed]
73. Nafissi, N.N.; Kosiorek, H.E.; Butterfield, R.J.; Moore, C.; Ho, T.; Singh, P.; Bryce, A.H. Evolving Natural History of Metastatic Prostate Cancer. *Cureus* **2020**, *12*, e11484. [CrossRef] [PubMed]
74. Maitland, N.J. Resistance to Antiandrogens in Prostate Cancer: Is It Inevitable, Intrinsic or Induced? *Cancers* **2021**, *13*, 327. [CrossRef] [PubMed]
75. Conteduca, V.; Caffo, O.; Fratino, L.; Lo Re, G.; Basso, U.; D'Angelo, A.; Donini, M.; Verderame, F.; Ratta, R.; Procopio, G.; et al. Impact of visceral metastases on outcome to abiraterone after docetaxel in castration-resistant prostate cancer patients. *Future Oncol.* **2015**, *11*, 2881–2891. [CrossRef] [PubMed]
76. Goodman, O.B., Jr.; Flaig, T.W.; Molina, A.; Mulders, P.F.; Fizazi, K.; Suttmann, H.; Li, J.; Kheoh, T.; de Bono, J.S.; Scher, H.I. Exploratory analysis of the visceral disease subgroup in a phase III study of abiraterone acetate in metastatic castration-resistant prostate cancer. *Prostate Cancer Prostatic Dis.* **2014**, *17*, 34–39. [CrossRef] [PubMed]
77. Poon, D.M.; Chan, K.; Lee, S.H.; Chan, T.W.; Sze, H.; Lee, E.K.; Lam, D.; Chan, M.F. Abiraterone acetate in metastatic castration-resistant prostate cancer—The unanticipated real-world clinical experience. *BMC Urol.* **2016**, *16*, 12. [CrossRef]

78. Moschini, M.; Sharma, V.; Zattoni, F.; Quevedo, J.F.; Davis, B.J.; Kwon, E.; Karnes, R.J. Natural History of Clinical Recurrence Patterns of Lymph Node-Positive Prostate Cancer After Radical Prostatectomy. *Eur. Urol.* **2016**, *69*, 135–142. [CrossRef]
79. Gandaglia, G.; Karakiewicz, P.I.; Briganti, A.; Passoni, N.M.; Schiffmann, J.; Trudeau, V.; Graefen, M.; Montorsi, F.; Sun, M. Impact of the Site of Metastases on Survival in Patients with Metastatic Prostate Cancer. *Eur. Urol.* **2015**, *68*, 325–334. [CrossRef]
80. Conteduca, V.; Crabb, S.J.; Jones, R.J.; Caffo, O.; Elliott, T.; Scarpi, E.; Fabbri, P.; Derosa, L.; Massari, F.; Numico, G.; et al. Persistent Neutrophil to Lymphocyte Ratio >3 during Treatment with Enzalutamide and Clinical Outcome in Patients with Castration-Resistant Prostate Cancer. *PLoS ONE* **2016**, *11*, e0158952. [CrossRef]
81. Armstrong, A.J.; Garrett-Mayer, E.; Ou Yang, Y.C.; Carducci, M.A.; Tannock, I.; de Wit, R.; Eisenberger, M. Prostate-specific antigen and pain surrogacy analysis in metastatic hormone-refractory prostate cancer. *J. Clin. Oncol.* **2007**, *25*, 3965–3970. [CrossRef]
82. Terada, N.; Akamatsu, S.; Okada, Y.; Negoro, H.; Kobayashi, T.; Yamasaki, T.; Matsui, Y.; Inoue, T.; Kamba, T.; Ogawa, O. Factors predicting efficacy and adverse effects of enzalutamide in Japanese patients with castration-resistant prostate cancer: Results of retrospective multi-institutional study. *Int. J. Clin. Oncol.* **2016**, *21*, 1155–1161. [CrossRef] [PubMed]
83. Shiota, M.; Yokomizo, A.; Adachi, T.; Koga, H.; Yamaguchi, A.; Imada, K.; Takeuchi, A.; Kiyoshima, K.; Inokuchi, J.; Tatsugami, K.; et al. The oncological outcomes and risk stratification in docetaxel chemotherapy for castration-resistant prostate cancer. *Jpn. J. Clin. Oncol.* **2014**, *44*, 860–867. [CrossRef]
84. Loriot, Y.; Bianchini, D.; Ileana, E.; Sandhu, S.; Patrikidou, A.; Pezaro, C.; Albiges, L.; Attard, G.; Fizazi, K.; De Bono, J.S.; et al. Antitumour activity of abiraterone acetate against metastatic castration-resistant prostate cancer progressing after docetaxel and enzalutamide (MDV3100). *Ann. Oncol.* **2013**, *24*, 1807–1812. [CrossRef] [PubMed]
85. Loriot, Y.; Fizazi, K.; de Bono, J.S.; Forer, D.; Hirmand, M.; Scher, H.I. Enzalutamide in castration-resistant prostate cancer patients with visceral disease in the liver and/or lung: Outcomes from the randomized controlled phase 3 AFFIRM trial. *Cancer* **2017**, *123*, 253–262. [CrossRef] [PubMed]
86. Penson, D.F.; Armstrong, A.J.; Concepcion, R.; Agarwal, N.; Olsson, C.; Karsh, L.; Dunshee, C.; Wang, F.; Wu, K.; Krivoshik, A.; et al. Enzalutamide Versus Bicalutamide in Castration-Resistant Prostate Cancer: The STRIVE Trial. *J. Clin. Oncol.* **2016**, *34*, 2098–2106. [CrossRef]
87. Davies, A.; Conteduca, V.; Zoubeidi, A.; Beltran, H. Biological Evolution of Castration-resistant Prostate Cancer. *Eur. Urol. Focus* **2019**, *5*, 147–154. [CrossRef]
88. Eisenberger, M.A.; Blumenstein, B.A.; Crawford, E.D.; Miller, G.; McLeod, D.G.; Loehrer, P.J.; Wilding, G.; Sears, K.; Culkin, D.J.; Thompson, I.M., Jr.; et al. Bilateral orchiectomy with or without flutamide for metastatic prostate cancer. *N. Engl. J. Med.* **1998**, *339*, 1036–1042. [CrossRef]
89. Corn, P.G. The tumor microenvironment in prostate cancer: Elucidating molecular pathways for therapy development. *Cancer Manag. Res.* **2012**, *4*, 183–193. [CrossRef]
90. Thompson, T.C.; Cunha, G.R.; Shannon, J.M.; Chung, L.W. Androgen-induced biochemical responses in epithelium lacking androgen receptors: Characterization of androgen receptors in the mesenchymal derivative of urogenital sinus. *J. Steroid. Biochem.* **1986**, *25*, 627–634. [CrossRef]
91. Ronnov-Jessen, L.; Petersen, O.W.; Bissell, M.J. Cellular changes involved in conversion of normal to malignant breast: Importance of the stromal reaction. *Physiol. Rev.* **1996**, *76*, 69–125. [CrossRef] [PubMed]
92. Liu, T.; Han, C.; Wang, S.; Fang, P.; Ma, Z.; Xu, L.; Yin, R. Cancer-associated fibroblasts: An emerging target of anti-cancer immunotherapy. *J. Hematol. Oncol.* **2019**, *12*, 86. [CrossRef] [PubMed]
93. Bauer, M.; Su, G.; Casper, C.; He, R.; Rehrauer, W.; Friedl, A. Heterogeneity of gene expression in stromal fibroblasts of human breast carcinomas and normal breast. *Oncogene* **2010**, *29*, 1732–1740. [CrossRef] [PubMed]
94. Monteran, L.; Erez, N. The Dark Side of Fibroblasts: Cancer-Associated Fibroblasts as Mediators of Immunosuppression in the Tumor Microenvironment. *Front. Immunol.* **2019**, *10*, 1835. [CrossRef]
95. Lee, S.W.; Kwak, H.S.; Kang, M.H.; Park, Y.Y.; Jeong, G.S. Fibroblast-associated tumour microenvironment induces vascular structure-networked tumouroid. *Sci. Rep.* **2018**, *8*, 2365. [CrossRef]
96. Leach, D.A.; Fernandes, R.C.; Bevan, C.L. Cellular specificity of androgen receptor, coregulators, and pioneer factors in prostate cancer. *Endocr. Oncol.* **2022**, *2*, R112–R131. [CrossRef]
97. Jenster, G. The role of the androgen receptor in the development and progression of prostate cancer. *Semin. Oncol.* **1999**, *26*, 407–421.
98. Leach, D.A.; Trotta, A.P.; Need, E.F.; Risbridger, G.P.; Taylor, R.A.; Buchanan, G. The prognostic value of stromal FK506-binding protein 1 and androgen receptor in prostate cancer outcome. *Prostate* **2017**, *77*, 185–195. [CrossRef]
99. Ricciardelli, C.; Choong, C.S.; Buchanan, G.; Vivekanandan, S.; Neufing, P.; Stahl, J.; Marshall, V.R.; Horsfall, D.J.; Tilley, W.D. Androgen receptor levels in prostate cancer epithelial and peritumoral stromal cells identify non-organ confined disease. *Prostate* **2005**, *63*, 19–28. [CrossRef]
100. Henshall, S.M.; Quinn, D.I.; Lee, C.S.; Head, D.R.; Golovsky, D.; Brenner, P.C.; Delprado, W.; Stricker, P.D.; Grygiel, J.J.; Sutherland, R.L. Altered expression of androgen receptor in the malignant epithelium and adjacent stroma is associated with early relapse in prostate cancer. *Cancer Res.* **2001**, *61*, 423–427.
101. Wikstrom, P.; Marusic, J.; Stattin, P.; Bergh, A. Low stroma androgen receptor level in normal and tumor prostate tissue is related to poor outcome in prostate cancer patients. *Prostate* **2009**, *69*, 799–809. [CrossRef] [PubMed]

102. Olapade-Olaopa, E.O.; MacKay, E.H.; Taub, N.A.; Sandhu, D.P.; Terry, T.R.; Habib, F.K. Malignant transformation of human prostatic epithelium is associated with the loss of androgen receptor immunoreactivity in the surrounding stroma. *Clin. Cancer Res.* **1999**, *5*, 569–576. [PubMed]
103. Li, Y.; Li, C.X.; Ye, H.; Chen, F.; Melamed, J.; Peng, Y.; Liu, J.; Wang, Z.; Tsou, H.C.; Wei, J.; et al. Decrease in stromal androgen receptor associates with androgen-independent disease and promotes prostate cancer cell proliferation and invasion. *J. Cell Mol. Med.* **2008**, *12*, 2790–2798. [CrossRef] [PubMed]
104. Huber, F.; Montani, M.; Sulser, T.; Jaggi, R.; Wild, P.; Moch, H.; Gevensleben, H.; Schmid, M.; Wyder, S.; Kristiansen, G. Comprehensive validation of published immunohistochemical prognostic biomarkers of prostate cancer -what has gone wrong? A blueprint for the way forward in biomarker studies. *Br. J. Cancer* **2015**, *112*, 140–148. [CrossRef]
105. Kristiansen, G. Markers of clinical utility in the differential diagnosis and prognosis of prostate cancer. *Mod. Pathol.* **2018**, *31*, S143–S155. [CrossRef]
106. Niu, Y.; Altuwaijri, S.; Lai, K.P.; Wu, C.T.; Ricke, W.A.; Messing, E.M.; Yao, J.; Yeh, S.; Chang, C. Androgen receptor is a tumor suppressor and proliferator in prostate cancer. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 12182–12187. [CrossRef]
107. Eagon, P.K.; Willett, J.E.; Seguiti, S.M.; Appler, M.L.; Gavaler, J.S.; Van Thiel, D.H. Androgen-responsive functions of male rat liver. Effect of chronic alcohol ingestion. *Gastroenterology* **1987**, *93*, 1162–1169. [CrossRef]
108. Eagon, P.K.; Elm, M.S.; Stafford, E.A.; Porter, L.E. Androgen receptor in human liver: Characterization and quantitation in normal and diseased liver. *Hepatology* **1994**, *19*, 92–100. [CrossRef]
109. Silva, A.F.; Abruzzese, G.A.; Ferrer, M.J.; Heber, M.F.; Ferreira, S.R.; Cerrone, G.E.; Motta, A.B. Fetal programming by androgen excess impairs liver lipid content and PPARg expression in adult rats. *J. Dev. Orig. Health Dis.* **2022**, *13*, 300–309. [CrossRef]
110. Chatterjee, B.; Song, C.S.; Kim, J.M.; Roy, A.K. Androgen and estrogen sulfotransferases of the rat liver: Physiological function, molecular cloning, and in vitro expression. *Chem. Biol. Interact.* **1994**, *92*, 273–279. [CrossRef]
111. Roy, A.K.; Milin, B.S.; McMinn, D.M. Androgen receptor in rat liver: Hormonal and developmental regulation of the cytoplasmic receptor and its correlation with the androgen-dependent synthesis of alpha2u-globulin. *Biochim. Biophys. Acta* **1974**, *354*, 213–232. [CrossRef] [PubMed]
112. Helms, T.H.; Mullins, R.D.; Thomas-Ahner, J.M.; Kulp, S.K.; Campbell, M.J.; Lucas, F.; Schmidt, N.; LeMoine, D.M.; Getaneh, S.; Xie, Z.; et al. Inhibition of androgen/AR signaling inhibits diethylnitrosamine (DEN) induced tumour initiation and remodels liver immune cell networks. *Sci. Rep.* **2021**, *11*, 3646. [CrossRef] [PubMed]
113. Andrisse, S.; Feng, M.; Wang, Z.; Awe, O.; Yu, L.; Zhang, H.; Bi, S.; Wang, H.; Li, L.; Joseph, S.; et al. Androgen-induced insulin resistance is ameliorated by deletion of hepatic androgen receptor in females. *FASEB J.* **2021**, *35*, e21921. [CrossRef] [PubMed]
114. Kanda, T.; Yokosuka, O. The androgen receptor as an emerging target in hepatocellular carcinoma. *J. Hepatocell Carcinoma* **2015**, *2*, 91–99. [CrossRef] [PubMed]
115. Flavell, R.A.; Sanjabi, S.; Wrzesinski, S.H.; Licona-Limon, P. The polarization of immune cells in the tumour environment by TGFbeta. *Nat. Rev. Immunol.* **2010**, *10*, 554–567. [CrossRef] [PubMed]
116. Xie, F.; Ling, L.; van Dam, H.; Zhou, F.; Zhang, L. TGF-beta signaling in cancer metastasis. *Acta Biochim. Biophys. Sin.* **2018**, *50*, 121–132. [CrossRef]
117. Hintz, H.M.; Gallant, J.P.; Vander Griend, D.J.; Coleman, I.M.; Nelson, P.S.; LeBeau, A.M. Imaging Fibroblast Activation Protein Alpha Improves Diagnosis of Metastatic Prostate Cancer with Positron Emission Tomography. *Clin. Cancer Res.* **2020**, *26*, 4882–4891. [CrossRef]
118. Delorey, T.M.; Ziegler, C.G.K.; Heimberg, G.; Normand, R.; Yang, Y.; Segerstolpe, A.; Abbondanza, D.; Fleming, S.J.; Subramanian, A.; Montoro, D.T.; et al. A single-cell and spatial atlas of autopsy tissues reveals pathology and cellular targets of SARS-CoV-2. *bioRxiv* **2021**. [CrossRef]
119. Guilliams, M.; Bonnardel, J.; Haest, B.; Vanderborght, B.; Wagner, C.; Remmerie, A.; Bujko, A.; Martens, L.; Thone, T.; Browaeys, R.; et al. Spatial proteogenomics reveals distinct and evolutionarily conserved hepatic macrophage niches. *Cell* **2022**, *185*, 379–396.e338. [CrossRef]
120. Bookout, A.L.; Jeong, Y.; Downes, M.; Yu, R.T.; Evans, R.M.; Mangelsdorf, D.J. Anatomical profiling of nuclear receptor expression reveals a hierarchical transcriptional network. *Cell* **2006**, *126*, 789–799. [CrossRef]
121. Nucci, R.A.B.; Teodoro, A.C.S.; Krause Neto, W.; Silva, W.A.; de Souza, R.R.; Anaruma, C.A.; Gama, E.F. Effects of testosterone administration on liver structure and function in aging rats. *Aging Male* **2017**, *20*, 134–137. [CrossRef] [PubMed]
122. Ohnishi, S.; Murakami, T.; Moriyama, T.; Mitamura, K.; Imawari, M. Androgen and estrogen receptors in hepatocellular carcinoma and in the surrounding noncancerous liver tissue. *Hepatology* **1986**, *6*, 440–443. [CrossRef] [PubMed]
123. Ma, W.L.; Lai, H.C.; Yeh, S.; Cai, X.; Chang, C. Androgen receptor roles in hepatocellular carcinoma, fatty liver, cirrhosis and hepatitis. *Endocr. Relat. Cancer* **2014**, *21*, R165–R182. [CrossRef] [PubMed]
124. Kalra, M.; Mayes, J.; Assefa, S.; Kaul, A.K.; Kaul, R. Role of sex steroid receptors in pathobiology of hepatocellular carcinoma. *World J. Gastroenterol.* **2008**, *14*, 5945–5961. [CrossRef]
125. Rooney, J.P.; Ryan, N.; Chorley, B.N.; Hester, S.D.; Kenyon, E.M.; Schmid, J.E.; George, B.J.; Hughes, M.F.; Sey, Y.M.; Tennant, A.; et al. From the Cover: Genomic Effects of Androstenedione and Sex-Specific Liver Cancer Susceptibility in Mice. *Toxicol. Sci.* **2017**, *160*, 15–29. [CrossRef] [PubMed]

126. Haider, A.; Gooren, L.J.; Padungtod, P.; Saad, F. Improvement of the metabolic syndrome and of non-alcoholic liver steatosis upon treatment of hypogonadal elderly men with parenteral testosterone undecanoate. *Exp. Clin. Endocrinol. Diabetes* **2010**, *118*, 167–171. [CrossRef]
127. Southren, A.L.; Gordon, G.G.; Olivo, J.; Rafii, F.; Rosenthal, W.S. Androgen metabolism in cirrhosis of the liver. *Metabolism* **1973**, *22*, 695–701. [CrossRef]
128. Xu, L.; Yuan, Y.; Che, Z.; Tan, X.; Wu, B.; Wang, C.; Xu, C.; Xiao, J. The Hepatoprotective and Hepatotoxic Roles of Sex and Sex-Related Hormones. *Front. Immunol.* **2022**, *13*, 939631. [CrossRef]
129. Dart, D.A.; Brooke, G.N.; Sita-Lumsden, A.; Waxman, J.; Bevan, C.L. Reducing prohibitin increases histone acetylation, and promotes androgen independence in prostate tumours by increasing androgen receptor activation by adrenal androgens. *Oncogene* **2012**, *31*, 4588–4598. [CrossRef]
130. Dart, D.A.; Waxman, J.; Aboagye, E.O.; Bevan, C.L. Visualising androgen receptor activity in male and female mice. *PLoS ONE* **2013**, *8*, e71694. [CrossRef]
131. Gamble, S.C.; Chotai, D.; Odontiadis, M.; Dart, D.A.; Brooke, G.N.; Powell, S.M.; Reebye, V.; Varela-Carver, A.; Kawano, Y.; Waxman, J.; et al. Prohibitin, a protein downregulated by androgens, represses androgen receptor activity. *Oncogene* **2007**, *26*, 1757–1768. [CrossRef] [PubMed]
132. Barbier-Torres, L.; Lu, S.C. Prohibitin 1 in liver injury and cancer. *Exp. Biol. Med.* **2020**, *245*, 385–394. [CrossRef] [PubMed]
133. Ko, K.S.; Tomasi, M.L.; Iglesias-Ara, A.; French, B.A.; French, S.W.; Ramani, K.; Lozano, J.J.; Oh, P.; He, L.; Stiles, B.L.; et al. Liver-specific deletion of prohibitin 1 results in spontaneous liver injury, fibrosis, and hepatocellular carcinoma in mice. *Hepatology* **2010**, *52*, 2096–2108. [CrossRef] [PubMed]
134. Manfredi, S.; Lepage, C.; Hatem, C.; Coatmeur, O.; Faivre, J.; Bouvier, A.M. Epidemiology and management of liver metastases from colorectal cancer. *Ann. Surg.* **2006**, *244*, 254–259. [CrossRef] [PubMed]
135. Gelfand, M.M.; Wiita, B. Androgen and estrogen-androgen hormone replacement therapy: A review of the safety literature, 1941 to 1996. *Clin. Ther.* **1997**, *19*, 383–404, discussion 367–388. [CrossRef]
136. Gild, P.; Cole, A.P.; Krasnova, A.; Dickerman, B.A.; von Landenberg, N.; Sun, M.; Mucci, L.A.; Lipsitz, S.R.; Chun, F.K.; Nguyen, P.L.; et al. Liver Disease in Men Undergoing Androgen Deprivation Therapy for Prostate Cancer. *J. Urol.* **2018**, *200*, 573–581. [CrossRef]
137. Yun, G.Y.; Kim, S.H.; Kim, S.W.; Joo, J.S.; Kim, J.S.; Lee, E.S.; Lee, B.S.; Kang, S.H.; Moon, H.S.; Sung, J.K.; et al. Atypical onset of bicalutamide-induced liver injury. *World J. Gastroenterol.* **2016**, *22*, 4062–4065. [CrossRef]
138. Richards, J.; Lim, A.C.; Hay, C.W.; Taylor, A.E.; Wingate, A.; Nowakowska, K.; Pezaro, C.; Carreira, S.; Goodall, J.; Arlt, W.; et al. Interactions of abiraterone, eplerenone, and prednisolone with wild-type and mutant androgen receptor: A rationale for increasing abiraterone exposure or combining with MDV3100. *Cancer Res.* **2012**, *72*, 2176–2182. [CrossRef]
139. James, N.D.; de Bono, J.S.; Spears, M.R.; Clarke, N.W.; Mason, M.D.; Dearnaley, D.P.; Ritchie, A.W.S.; Amos, C.L.; Gilson, C.; Jones, R.J.; et al. Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy. *N. Engl. J. Med.* **2017**, *377*, 338–351. [CrossRef]
140. Ryan, C.J.; Smith, M.R.; Fizazi, K.; Saad, F.; Mulders, P.F.; Sternberg, C.N.; Miller, K.; Logothetis, C.J.; Shore, N.D.; Small, E.J.; et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): Final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol.* **2015**, *16*, 152–160. [CrossRef]
141. Fizazi, K.; Scher, H.I.; Molina, A.; Logothetis, C.J.; Chi, K.N.; Jones, R.J.; Staffurth, J.N.; North, S.; Vogelzang, N.J.; Saad, F.; et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: Final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol.* **2012**, *13*, 983–992. [CrossRef] [PubMed]
142. Fizazi, K.; Tran, N.; Fein, L.; Matsubara, N.; Rodriguez-Antolin, A.; Alekseev, B.Y.; Ozguroglu, M.; Ye, D.; Feyerabend, S.; Protheroe, A.; et al. Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer. *N. Engl. J. Med.* **2017**, *377*, 352–360. [CrossRef] [PubMed]
143. Colomba, E.; Marret, G.; Baciarello, G.; Lavaud, P.; Massard, C.; Loriot, Y.; Albiges, L.; Carton, E.; Alexandre, J.; Huillard, O.; et al. Liver tests increase on abiraterone acetate in men with metastatic prostate cancer: Natural history, management and outcome. *Eur. J. Cancer* **2020**, *129*, 117–122. [CrossRef] [PubMed]
144. Guo, Y.; Ji, X.; Liu, J.; Fan, D.; Zhou, Q.; Chen, C.; Wang, W.; Wang, G.; Wang, H.; Yuan, W.; et al. Effects of exosomes on pre-metastatic niche formation in tumors. *Mol. Cancer* **2019**, *18*, 39. [CrossRef]
145. Paget, S. The distribution of secondary growths in cancer of the breast. 1889. *Cancer Metastasis Rev.* **1989**, *8*, 98–101.
146. Langley, R.R.; Fidler, I.J. The seed and soil hypothesis revisited–the role of tumor-stroma interactions in metastasis to different organs. *Int. J. Cancer* **2011**, *128*, 2527–2535. [CrossRef]
147. Sorensen, H.T.; Friis, S.; Olsen, J.H.; Thulstrup, A.M.; Mellemkjaer, L.; Linet, M.; Trichopoulos, D.; Vilstrup, H.; Olsen, J. Risk of liver and other types of cancer in patients with cirrhosis: A nationwide cohort study in Denmark. *Hepatology* **1998**, *28*, 921–925. [CrossRef]
148. Burnier, J.V.; Wang, N.; Michel, R.P.; Hassanain, M.; Li, S.; Lu, Y.; Metrakos, P.; Antecka, E.; Burnier, M.N.; Ponton, A.; et al. Type IV collagen-initiated signals provide survival and growth cues required for liver metastasis. *Oncogene* **2011**, *30*, 3766–3783. [CrossRef]

149. Eveno, C.; Hainaud, P.; Rampanou, A.; Bonnin, P.; Bakhouche, S.; Dupuy, E.; Contreres, J.O.; Pocard, M. Proof of prometastatic niche induction by hepatic stellate cells. *J. Surg. Res.* **2015**, *194*, 496–504. [CrossRef]
150. Nielsen, S.R.; Quaranta, V.; Linford, A.; Emeagi, P.; Rainer, C.; Santos, A.; Ireland, L.; Sakai, T.; Sakai, K.; Kim, Y.S.; et al. Macrophage-secreted granulin supports pancreatic cancer metastasis by inducing liver fibrosis. *Nat. Cell Biol.* **2016**, *18*, 549–560. [CrossRef]
151. Xie, Z.; Gao, Y.; Ho, C.; Li, L.; Jin, C.; Wang, X.; Zou, C.; Mao, Y.; Wang, X.; Li, Q.; et al. Exosome-delivered CD44v6/C1QBP complex drives pancreatic cancer liver metastasis by promoting fibrotic liver microenvironment. *Gut* **2022**, *71*, 568–579. [CrossRef] [PubMed]
152. Arriazu, E.; Ruiz de Galarreta, M.; Cubero, F.J.; Varela-Rey, M.; Perez de Obanos, M.P.; Leung, T.M.; Lopategi, A.; Benedicto, A.; Abraham-Enachescu, I.; Nieto, N. Extracellular matrix and liver disease. *Antioxid. Redox. Signal.* **2014**, *21*, 1078–1097. [CrossRef] [PubMed]
153. Ohlund, D.; Elyada, E.; Tuveson, D. Fibroblast heterogeneity in the cancer wound. *J. Exp. Med.* **2014**, *211*, 1503–1523. [CrossRef] [PubMed]
154. Khazali, A.S.; Clark, A.M.; Wells, A. Inflammatory cytokine IL-8/CXCL8 promotes tumour escape from hepatocyte-induced dormancy. *Br. J. Cancer* **2018**, *118*, 566–576. [CrossRef] [PubMed]
155. Pickup, M.W.; Mouw, J.K.; Weaver, V.M. The extracellular matrix modulates the hallmarks of cancer. *EMBO Rep.* **2014**, *15*, 1243–1253. [CrossRef]
156. Costa-Silva, B.; Aiello, N.M.; Ocean, A.J.; Singh, S.; Zhang, H.; Thakur, B.K.; Becker, A.; Hoshino, A.; Mark, M.T.; Molina, H.; et al. Pancreatic cancer exosomes initiate pre-metastatic niche formation in the liver. *Nat. Cell Biol.* **2015**, *17*, 816–826. [CrossRef]
157. Wang, Y.; Tu, K.; Liu, D.; Guo, L.; Chen, Y.; Li, Q.; Maiers, J.L.; Liu, Z.; Shah, V.H.; Dou, C.; et al. p300 Acetyltransferase Is a Cytoplasm-to-Nucleus Shuttle for SMAD2/3 and TAZ Nuclear Transport in Transforming Growth Factor beta-Stimulated Hepatic Stellate Cells. *Hepatology* **2019**, *70*, 1409–1423. [CrossRef]
158. Houg, D.S.; Bijlsma, M.F. The hepatic pre-metastatic niche in pancreatic ductal adenocarcinoma. *Mol. Cancer* **2018**, *17*, 95. [CrossRef]
159. Perl, A.K.; Wilgenbus, P.; Dahl, U.; Semb, H.; Christofori, G. A causal role for E-cadherin in the transition from adenoma to carcinoma. *Nature* **1998**, *392*, 190–193. [CrossRef]
160. Sethi, T.; Rintoul, R.C.; Moore, S.M.; MacKinnon, A.C.; Salter, D.; Choo, C.; Chilvers, E.R.; Dransfield, I.; Donnelly, S.C.; Strieter, R.; et al. Extracellular matrix proteins protect small cell lung cancer cells against apoptosis: A mechanism for small cell lung cancer growth and drug resistance in vivo. *Nat. Med.* **1999**, *5*, 662–668. [CrossRef]
161. Yang, L.; Li, T.; Shi, H.; Zhou, Z.; Huang, Z.; Lei, X. The cellular and molecular components involved in pre-metastatic niche formation in colorectal cancer liver metastasis. *Expert. Rev. Gastroenterol. Hepatol.* **2021**, *15*, 389–399. [CrossRef] [PubMed]