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TOPIC PAPER

Developments in oligometastatic hormone-sensitive prostate cancer

Ken Chow[1,2] · Patrick McCoy[1] · Ryan Stuchbery[3] · Niall M. Corcoran[1,2,3] · Christopher M. Hovens[1,3]

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Abstract

Purpose To review the current understanding and recent developments regarding the concept of oligometastases in hormone-sensitive prostate cancer.

Methods A comprehensive literature search of electronic databases, including PubMed and Embase was conducted for the search term 'oligometastases' in combinations with 'prostate cancer', 'hormone sensitive', 'genetics', and 'molecular'. All articles relating to these search terms have been taken into account.

Results Prostate cancer remains a major cause of morbidity and mortality worldwide. The majority of these cancer-related deaths result from metastases. Currently, there is a dichotomy in prostate cancer management where it is only deemed curable if it is localized, while any signs of metastasis relegate patients to systemic therapies to delay their inevitable death. A growing body of evidence supports the notion that aggressive treatments during the stable 'oligometastatic' state can have significant clinical benefits and potentially 'reset' prostate cancer to an earlier time point in cancer progression. This concept of oligometastases has been adopted in other cancer settings such as colorectal and non-small-cell lung cancers.

Conclusion Multiple clinical and molecular biological studies have been influential in the support of a stable state in metastatic cancer progression coined 'oligometastases'. As our understanding of oligometastases in hormone-sensitive prostate cancer develops, we will be able to molecularly define the oligometastatic state and develop clinically available diagnostic tests. In doing so, prostate cancer patients will experience significant clinical benefits and the burden of prostate cancer worldwide will likely be reduced.

Keywords Oligometastases · Metastasis · Prostate cancer · Hormone sensitive · Genetics · Review

Introduction

Cancer remains a major cause of morbidity and mortality worldwide with an estimated 14 million new cases and 8 million cancer-related deaths in 2012. Out of those global statistics, 1.1 million men were diagnosed with prostate cancer, while 307,000 men died from the disease [1]. Despite advances in surgical, medical, and radiation therapies, the vast majority of these cancer-related deaths result from the progression and spread of metastases [2].

In the current medical environment, there is a dichotomy of management standards where only localized tumors are considered curable, while patients with any sign of metastatic spread (regional or distant) are typically only offered systemic treatment modalities for delaying inevitable palliation. This is strongly evident in current prostate cancer management guidelines. Men who present with metastatic prostate cancer at time of diagnosis are usually only recommended systemic treatments such as androgen deprivation therapy; while localized treatment of the primary tumor in these men is still regarded as experimental [3]. These attitudes arise from the firmly held belief that tumors are either localized or systemic.

Ever since the concept of 'oligometastases' was first proposed by Hellman and Weichselbaum in 1995, there has been a slow shift in the metastasis paradigm [4]. Their theory states that the dissemination of cancer sits on a

✉ Christopher M. Hovens
chovens@unimelb.edu.au

[1] Department of Surgery, The University of Melbourne, 5th Floor Clinical Sciences Building, Royal Melbourne Hospital, Grattan Street, Parkville, VIC, Australia

[2] Department of Urology, Royal Melbourne Hospital, Parkville, VIC, Australia

[3] Australian Prostate Cancer Research Centre Epworth, Richmond, VIC, Australia

biological spectrum existing between localized and systemic disease; at the time of diagnosis, metastatic cancer can be at an intermediate state where there are limited number of metastases and metastatic sites. At this point, the clones that give rise to these lesions have not yet acquired their full metastatic potential [5]. There is a growing body of evidence demonstrating that it is possible to improve progression-free survival (PFS), cancer-specific survival (CSS) and overall survival (OS) by offering aggressive treatments to patients while in this limited oligometastatic state [6].

However, despite the increasing acceptance of the concept of oligometastases, the accepted number and sites of metastases that count as being oligometastatic are still widely debated amongst experts in the field [6]. At the recent Advanced Prostate Cancer Consensus Conference 2017, a panel of 61 invited experts from 21 countries convened to discuss this controversial topic; however, they were unable to reach a consensus on the limits of the disease state. Regarding the sites of metastasis which would be included in oligometastatic prostate cancer, 61% of the panel voted for the inclusion of bone and/or lymph node, 10% for lymph node only, 13% for any location (including visceral metastasis), and 10% did not support the concept of oligometastases [7]. Out of the supporters for oligometastatic disease, a vote was cast for the cut-off number of metastases before the disease was no longer deemed oligometastatic. 14, 66, and 20% voted for ≤ 2 metastases, ≤ 3 metastases, and ≤ 5 metastases, respectively. There are also further variations to oligometastatic disease which are not contentious and include time of oligometastatic onset, whether the disease is synchronous (identified at time of diagnosis) versus metachronous (appearance after the initial treatment of the primary tumor); and castration-naïve versus castration-resistant oligometastatic disease [6]. Another complicating factor in defining oligometastases in prostate cancer is the ongoing advances in imaging technologies which have delivered greater sensitivity and specificity. This has allowed metastatic sites which would not have been identified on traditional imaging modalities such as computed tomography (CT) and ^{99}mTc-Bone scan to now be seen on C-11 choline and prostate-specific membrane antigen-based PET/CT. This means that the defining features of oligometastases regarding number and location are constantly changing. Patients who previously would have been diagnosed with localized disease may now be diagnosed with metastatic disease and be faced with the different therapeutic options that entails.

Despite the lack of consensus in the professional community regarding the exact definition of oligometastases in prostate cancer, it is important to further explore its significance as a metastatic state. This involves understanding whether the oligometastatic lesions are due to cancer clones of limited metastatic potential which continue towards polymetastases once they have acquired further necessary mutations; or it may be a completely unrelated entity to polymetastases. This review aims to demonstrate the rationale for supporting the oligometastatic state and present the current literature regarding the genetic landscape that potentially determines oligometastases in castrate-naïve prostate cancer.

Clinical evidence for the existence of an oligometastatic state in cancers

There has been a growing body of clinical literature in support of the oligometastatic state concept whereby locally ablative therapies in limited metastatic patients have resulted in improved progression-free survival and potential cure. Before this concept was introduced into the field of prostate cancer, a majority of the work was pioneered in other fields including colorectal and lung cancer.

Support for the concept of the oligometastatic state arose from studies investigating the benefits of liver resections for metastases in colorectal cancers. Reports from multiple centers demonstrated 5-year survivals of 23–39% for patients who underwent complete resection of detectable liver metastases [8–12]. This is especially remarkable given that patients with unresected liver metastases have a median survival of 6–9 months at the time [13, 14]. Kanas et al. performed a meta-analysis on 60 contemporary published studies from 1999 to 2010 that demonstrated median 5- and 10-year survival rates of 38% and 26%, respectively, with liver metastasis resection [15]. The culmination of these studies has led the European Society for Medical Oncology to release a consensus statement recognizing the oligometastatic state in colorectal cancers [16].

Additionally, investigation into the resection of pulmonary metastasis contributed to building support for the oligometastatic state early in its conception. The International Registry of Lung Metastases was first established in 1991 comprising of 18 institutions across Europe and North America. Their aim was to collect information regarding long-term outcomes of lung resection for metastases; these included metastases arising from primary tumors of epithelial, sarcoma, germ cell, and melanoma origins. In 1997, they published the results of 5206 cases of lung metastasectomy; 4572 of these cases achieved complete resection, while 634 had either macroscopic or microscopic residual disease [17]. Due to this difference, an interesting variation in 5-year survival was observed; 36% for complete resection versus 13% for incomplete resection. This distinction was also seen in 10-year survival rates of 26% and 7% for complete and incomplete resection, respectively.

Non-small-cell lung cancer (NSCLC) is another area in which the oligometastatic state has gained significant traction. This is not surprising as approximately 20–50% of newly diagnosed NSCLC patients present with metastatic

disease and the median OS for these patients is 7–11 months [18, 19]. This recognition of the oligometastatic state is reflected in the recent ESMO Clinical Practice Guidelines for Metastatic NSCLC as it is stated that patients with solitary metastases to the brain, adrenals, or lung can be treated with curative intent [19]. The review by Pfannschmidt et al. highlights this notion in the treatment of solitary brain metastases in NSCLC observing a median OS after resection across 8 studies of 7–27 months, and 5-year survival rates of 8–21% [18]. This is in comparison to the meager median overall survival of only 1–2 months for untreated brain metastases [20]. Gomez et al. conducted a multicenter, randomized, controlled, phase 2 study comparing local consolidative therapy (chemotherapy combined with surgery and/or radiotherapy) to standard-of-care maintenance treatment. This trial was terminated early on annual analyses as the local consolidative therapy group had significantly longer median progression-free survival relative to the maintenance treatment group (11.9 versus 3.9 months, $p=0.0054$) [21]. Recently, similar results were also seen in the randomized phase 2 study by Iyengar et al. [22]. They demonstrated significant improvements in patients undergoing non-invasive stereotactic ablative radiotherapy followed by maintenance chemotherapy compared to maintenance chemotherapy alone (9.7 versus 3.5 months, $p=0.01$).

After the pioneering work across multiple cancers investigating the resection of metastases from liver, lung, and brain, as well as its acceptance by experts in those fields, a path was created to explore the oligometastatic theory in the field of prostate cancer.

Local treatment of oligometastases improves clinical outcomes in prostate cancer

Conventionally, radical prostatectomy and external beam radiotherapy (EBRT) have only been offered with curative intent in patients with localized prostate cancer due to the morbidity involved [3]. This standard is slowly evolving as the concept of treatable oligometastases is becoming increasingly accepted; as well as advancements in therapeutic technologies and techniques in prostate cancer leading to much lower associated morbidity [5, 23]. These techniques are mainly minimally invasive surgeries and stereotactic body radiotherapy (SBRT). Like other cancers, there are a growing number of studies supporting the treatment of limited metastatic disease as evidence is showing improved PFS and delayed onset of castration resistance [6, 24].

Culp et al. utilized the population-based registries data gathered in the Surveillance Epidemiology and End Results (SEER) database to identify 8185 men with stage IV metastatic prostate cancer at time of diagnosis between 2004 and 2010 [25]. These men were divided into groups pertaining to radical prostatectomy, brachytherapy, and no surgery/radiation therapy. Culp et al. demonstrated 5-year OS of 67.4% in radical prostatectomy and 52.6% in brachytherapy; this was significantly higher than the 22.5% in the no surgery/radiation therapy cohort. These results were also mirrored in the Munich Cancer Registry data. Out of 1538 patients with newly diagnosed metastatic prostate cancer, the patients who underwent radical prostatectomy had significantly higher 5-year OS rates of 55% compared to 21% of those who did not have local surgical treatment ($p=<0.01$) [26]. Limitations of these studies included not being able to fully control for selection bias as certain variables were unavailable in these cancer registries such as comorbidities, performance status, as well as timing/dosage of chemotherapy and/or ADT. Nonetheless, these results assisted in paving the way for further research into local-directed therapies in metastatic prostate cancer.

One of these studies by Heidenreich et al. in 2015 investigated whether there was any value in performing cytoreductive radical prostatectomy for prostate cancer patients with 3 or fewer osseous metastases. A total of 23 patients were included in their treatment arm, while another group with matching clinical, biological, and oncological characteristics was assigned as controls. In comparison between treatment and control groups, this study demonstrated longer median time for the development of castration resistance (40 versus 29 months, $p=0.032$) and improved clinical PFS (38.6 versus 26.5 months, $p=0.032$), and CSS (95.6% versus 84.2%, $p=0.043$) [27]. Cho et al. explored a similar question in 140 metastatic prostate cancer patients using localized radiotherapy to treat the primary tumor compared to no localized treatment. They found that the radiotherapy cohort had better 3-year OS (69% versus 43%, $p=0.004$) and biochemical PFS (52% versus 16%, $p=0.002$) [28], which highlights once again the existence of a limited stable metastatic disease state in prostate cancer and the benefits of primary tumor control.

In addition to primary tumor control, metastases-directed therapy with surgical salvage lymph node dissection or radiotherapy modalities can also be employed. In the review by Koo et al., three studies into salvage lymph node dissection in oligometastatic prostate cancer were assessed. It was reported that up to 29, 52, and 89% achieved biochemical recurrence-free survival, PFS, and CSS, respectively [24]. The results from studies on the use of radiotherapy modalities, such as EBRT and SBRT, for metastases-directed treatment in oligometastatic prostate cancer were also reported by Koo et al. and Tosoian et al. It was found that SBRT has the ability to demonstrate local control rates up to 92% at 5-years and 5-year OS of up to 88% [6, 24]. A recent prospective, randomized, multicenter trial described by Ost et al. investigated the potential benefits of metastases-directed therapy

in patients with up to three extracranial metastases who have already received localized treatment with curative intent. The median ADT-free survival for the metastases-directed therapy group was 21 months compared to 13 months for the surveillance group [29].

Clinically, the growing body of literature reporting the use of local- and metastases-directed therapies against metastatic prostate cancer and demonstrating improved survival indicators only strengthens the existence of a stable, limited metastatic state. By implementing aggressive treatments at this metaphoric 'pause' in metastatic progression, it is possible that the responsible oligometastatic cancer clones with limited metastatic potential are eliminated. This essentially resets the disease to an earlier time point on the metastasis spectrum requiring the remaining low-metastatic-potential cancer clones to reacquire metastatic mutations before the disease can continue to advance. With the clinical rationale for such a state being explored, it is only natural that genetic and biological studies follow.

A genetic viewpoint on the formation of oligometastatic disease

The development of metastasis and the genetic relationship between metastatic sites is a contentious issue. There are currently two contrary explanations for the existence of an oligometastatic state. The first posits that oligometastases have clones originating from the primary site of cancer which possess unique genetic differences compared to polymetastatic disease; therefore, aggressive control of the primary will prevent further development and dissemination. The second theory proposes that oligometastatic disease is a transient stable state before developing into a polymetastatic state, with foundation oligometastatic sites continuing to 'self-seed' further metastases throughout the body. The first theory suggests that a distinction between oligometastatic and polymetastatic disease is encoded on the genetic level before metastatic spread occurs; whereas the second theory, which has become more widely accepted, suggests that metastasis is a multi-step process with ongoing mutational evolution occurring at the site of oligometastases, thus leading to the development of polymetastatic disease. Unfortunately, no current studies addressing genetic alterations in oligometastatic disease have been able to demonstrate which mechanism is correct, although they are not necessarily mutually exclusive. This highlights a significant gap in the current understanding of oligometastases; not only for prostate cancer, but for the field of cancer as a whole.

Additionally, as it has been proposed that oligometastatic states can have different origins, it follows that each different class would have distinct genetic characteristics. Tree et al. separated oligometastatic patients into three distinct groups; synchronous, metachronous, and patients whose oligometastatic disease is the result of cytoreductive therapy applied to polymetastatic sites [30]. Each of these oligometastatic subtypes would have distinct genetic drivers, each reflecting their clonal origins from differing disease stages and the impact of various treatments.

Oligometastases as a genetic staging ground for further metastatic spread

Despite the number of challenges involved in the genetic analysis of oligometastatic lesions, several studies have attempted to reveal the genetic landscape of oligometastases. Studies in pancreatic cancer showed that oligometastatic sites were largely genetically identical to primary tumors, while unique genetic differences were demonstrated as the disease progressed towards a polymetastatic state [31, 32]. Further evidence of oligometastases as a metastatic staging ground has been seen in clear-cell renal carcinoma. A study by Gerlinger et al. showed that many metastatic sites had ancestral clones from the primary tumor, while some sites seemed to show ancestral origins from other metastatic lesions [33]. It should also be noted that tumor cells in polymetastatic clear-cell renal carcinoma patients compared to those with oligometastatic disease expressed higher levels of PBK, BIRC5 and PTTG1. These proteins are responsible for cell division and proliferation, potentially indicating the acquisition of mutations required for polymetastatic disease [34]. Accordingly, each of these findings supports the notion that oligometastatic sites are clonally similar to the primary and serve as an intermediate stage for polymetastatic disease. Further support for the concept of differential molecular subtypes for distinct metastatic states has been provided by Pitroda et al. who performed multivariable genome-wide analysis investigating genetic subtypes of oligometastatic sites in the liver of colorectal cancer patients. They were able to successfully identify genetic differences between patients with oligo- and polymetastatic disease, and were successful in subtyping liver metastases based on clinical outcomes [35]. Polymetastatic tumors exhibited *VEGFA* amplification in concert with stromal, mesenchymal, and angiogenic signatures, or alternatively had unique *NOTCH1* and *PIK3C2B* mutations with E2F/MYC activation [35].

Possibly, the most significant advance in recent years regarding understanding the molecular differences between oligometastatic and polymetastatic disease is the identification of the role of microRNAs in the development of metastases. A study conducted by Lussier et al. on 63 metastatic lung cancers compared the microRNA expression profiles between oligometastatic and polymetastatic patients; they were able to identify unique microRNA expression profiles for both oligometastatic and polymetastatic patients. Further

refinement resulted in a panel of 29 microRNAs that was able to clearly separate oligometastatic and polymetastatic patients [36]. A pilot study investigating in part whether microRNAs can be used as a prognostic marker of response to SBRT in oligometastatic lung cancer patients found that a 3-microRNA classifier could significantly separate OS of > 3 years in their cohort. However, due to small sample size, these data are not particularly strong and require further validation [37]. While this indicates that differences exist in the microRNA profiles between oligometastatic and polymetastatic diseases, its clinical utility remains unclear.

Interestingly, almost all microRNAs that have been found to be overexpressed in oligometastatic samples compared to polymetastatic sites have tumor-suppressive properties affecting proliferation, epithelial mesenchymal transition (EMT), invasion, and motility [38]. This suggests that microRNAs are directly involved in preventing the development of polymetastatic disease. miR-29c and miR-655 have been observed in separate studies to both be upregulated in oligometastatic disease compared to polymetastatic disease, suppressing metastatic potential by targeting genes required for TGF-β-induced EMT [39, 40]. microRNAs upregulated in oligometastatic sites have been shown to exert tumor-suppressing effects through a number of mechanisms. miR-125a has been shown to down-regulate kinases that are responsible for increased cell invasion [41], miR-485 has been shown to prevent cancer cell migration through the inhibition of colony formation in vitro [42], and in vivo investigations of miR-296 have shown that it also reduces cancer cell mobility with loss of miR-296 causing increased cancer cell invasiveness [43]. Moving away from tumor suppressors, an interesting group of three microRNAs belonging to the mir-200 family were detected to be upregulated in polymetastases by a group from the University of Chicago. They explored the hypothesis that by upregulating certain microRNAs, it might be possible to switch the tumor phenotype from oligometastatic to polymetastatic; they tested this using oligo- and polymetastatic clones in mouse melanoma B16 and human MB-435 breast cancer models [38]. They found that the overexpression of mir-200c led to a switch from oligometastases to polymetastases, and that these cells had higher metastatic potential. This finding regarding mir-200c is also supported by two further studies in breast cancer models [44, 45].

Taken together, these studies show that microRNAs may have a profound effect on the metastatic state. As such, it would imply that if oligometastatic disease is a transient state before the development of more extensive polymetastatic disease, then changes in the expression levels of certain microRNA expression would be an important stage in the evolution of polymetastatic disease. If true, then a microRNA profile of metastatic sites may serve as a useful prognostic marker in metastatic cancer patients at risk of polymetastatic disease progression. However, the clinical translation of microRNA assays into the diagnostic and/or prognostic setting has been fraught [46], the main confounder being the lack of specificity of microRNA expression to the disease setting.

The challenges facing the genetic investigation of oligometastatic prostate cancer

Like many other cancers, a genetic signature of oligometastatic prostate cancer has yet to be established due to a lack of research. These analyses in prostate cancer are particularly challenging due to the high levels of inter-patient and intratumoral genetic heterogeneity that are characteristics of the disease. The subclonal origins of metastatic prostate cancer were investigated in great depth by Hong et al. which showed that metachronous metastatic prostate cancer could arise from any number of clones in the heterogeneous primary disease, not just the dominant clone. Additionally, the authors demonstrated cross-seeding between metastatic sites as well as metastatic self-seeding; therefore, leading to dynamic remodeling of subclonal mixtures and further supporting the dynamic nature of the development of metastatic disease [47]. As this study utilized longitudinal and multi-region sampling of metastases, it represents the metachronous nature of metastatic prostate cancer following treatment of localized prostate cancer with curative intent. Given that these patients did not receive metastatic-directed therapy, additional longitudinal genetic investigations are required in metastatic-direct therapy patients to further understand the genetic landscape of metachronous oligometastatic prostate cancer. Metastatic prostate cancer shows a strong preference for metastasising to bone [48], potentially indicating the microenvironmental requirements for the development of polymetastatic disease. While there remains much work to be completed in the genetic investigation of prostate cancer oligometastases, answering these questions is an important step towards better treatment practices, with highly evident clinical benefits.

The role of metastatic cell dormancy in oligometastatic disease

The concept of undetected dormant metastatic cells in cancer, including prostate cancer, is not a new theory. Research into tumor cell dormancy, also known as micrometastasis, spans back over four decades [49]. The majority of cancer cells that have migrated away from the primary tumor appear to lack the metastatic potential to effectively colonize a distant site and in several cancer types, single cancer

cells can be detected in blood and bone marrow years before metastatic tumors are detected [50]. Similarly, it has been demonstrated in prostate cancer that once cancer cells have implanted into the bone microenvironment, BMP7 secreted from the bone stromal cells induces metastatic cell senescence [51]. Despite this dormancy, some studies have found the presence of micrometastasis to be significantly associated with poorer clinical outcomes [50, 52].

Due to its dormant nature as well as its potential to be widely dispersed and linked to adverse disease outcomes, it is currently unclear whether micrometastasis is more reflective of oligometastases or early stages of polymetastatic disease. The potential impact of micrometastasis on the outcomes of oligometastatic disease is an important area for further investigation, especially as it is possible that the same mechanisms that create small, dormant metastatic sites may also be the cause of the slower growing properties related to oligometastatic sites and their restricted metastatic potential.

Conclusion

Overall, the evidence surrounding oligometastases, especially in hormone-sensitive prostate cancer, is continually growing and generating greater interest. At this point in time, there is no consensus in the scientific or clinical community for the exact definition in prostate cancer regarding the number and sites of oligometastatic lesions. This is likely to be an ongoing issue, with consequent uncertainty in determining the appropriate standard of care for these patients, especially as imaging techniques develop with greater sensitivity and specificity. However, if a specific genetic profile that is unique to the oligometastatic state is identified, this could potentially permit the development of a clinical diagnostic test. This will be pivotal as current evidence paints a picture that oligometastases relates to a stable time point in metastatic progression, a metaphoric 'pause', where aggressive treatment to the primary tumor and oligometastatic sites has the potential for clinical benefits. This may 'reset' the clock on disease progression and increase rates of stable metastatic disease. Additional studies will be required to further elucidate the oligometastatic state and its treatment.

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References

1. Stewart BW, Wild CP (2014) World Cancer Report 2014. Lyon, France: International Agency for Research on Cancer. World Health Organization 630
2. Langley RR, Fidler IJ (2007) Tumor cell-organ microenvironment interactions in the pathogenesis of cancer metastasis. Endocr Rev 28:297–321
3. Mottet N, van den Bergh RCN, Briers E et al (2018) EAU Guidelines. Edn. presented at the EAU Annual Congress Copenhagen 2018. EAU Guidelines Office, Arnhem, The Netherlands
4. Hellman S, Weichselbaum RR (1995) Oligometastases. J Clin Oncol 13:8–10
5. Reyes DK, Pienta KJ (2015) The biology and treatment of oligometastatic cancer. Oncotarget 6:8491–8524
6. Tosoian JJ, Gorin MA, Ross AE et al (2017) Oligometastatic prostate cancer: definitions, clinical outcomes, and treatment considerations. Nat Rev Urol 14:15–25
7. Gillessen S, Attard G, Beer TM et al (2018) Management of patients with advanced prostate cancer: the Report of the Advanced Prostate Cancer Consensus Conference APCCC 2017. Eur Urol 73:178–211
8. Nordlinger B, Quilichini MA, Parc R et al (1987) Hepatic resection for colorectal liver metastases. Influence on survival of preoperative factors and surgery for recurrences in 80 patients. Ann Surg 205:256–263
9. Hughes KS, Rosenstein RB, Songhorabodi S et al (1988) Resection of the liver for colorectal carcinoma metastases. Dis Colon Rectum 31:1–4
10. Gayowski TJ, Iwatsuki S, Madariaga JR et al (1994) Experience in hepatic resection for metastatic colorectal cancer: analysis of clinical and pathologic risk factors. Surgery 116:703–710 **(discussion 710–1)**
11. Scheele J, Stang R, Altendorf-Hofmann A, Paul M (1995) Resection of colorectal liver metastases. World J Surg 19:59–71
12. Fong Y, Cohen AM, Fortner JG et al (1997) Liver resection for colorectal metastases. J Clin Oncol 15:938–946
13. Rougier PH, Milan C, Lazorthes F et al (1995) Prospective study of prognostic factors in patients with unresected hepatic metastases from colorectal cancer. Br J Surg 82:1397–1400
14. Fong Y, Fortner J, Sun RL et al (1999) Clinical score for predicting recurrence after hepatic resection for metastatic colorectal

cancer: analysis of 1001 consecutive cases. Ann Surg 230:309–318 **(discussion 318–21)**
15. Kanas GP, Taylor A, Primrose JN et al (2012) Survival after liver resection in metastatic colorectal cancer: review and meta-analysis of prognostic factors. Clin Epidemiol 4:283–301
16. Van Cutsem E, Cervantes A, Adam R et al (2016) ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol 27:1386–1422
17. Pastorino U, Buyse M, Friedel G et al (1997) Long-term results of lung metastasectomy: prognostic analyses based on 5206 cases. J Thorac Cardiovasc Surg 113:37–49
18. Pfannschmidt J, Dienemann H (2010) Surgical treatment of oligometastatic non-small cell lung cancer. Lung Cancer 69:251–258
19. Peters S, Adjei AA, Gridelli C et al (2012) Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 23(Suppl 7):56–64
20. Richards P, McKISSOCK W (1963) Intracranial metastases. Br Med J 1:15–18
21. Gomez DR, Blumenschein GR Jr, Lee JJ et al (2016) Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study. Lancet Oncol 17:1672–1682
22. Iyengar P, Wardak Z, Gerber DE et al (2018) Consolidative radiotherapy for limited metastatic non-small-cell lung cancer: a phase 2 randomized clinical trial. JAMA Oncol 4:e173501
23. Yao HH, Hong MK, Corcoran NM et al (2014) Advances in local and ablative treatment of oligometastasis in prostate cancer. Asia Pac J Clin Oncol 10:308–321
24. Koo KC, Dasgupta P (2018) Treatment of oligometastatic hormone-sensitive prostate cancer: a comprehensive review. Yonsei Med J 59:567–579
25. Culp SH, Schellhammer PF, Williams MB (2014) Might men diagnosed with metastatic prostate cancer benefit from definitive treatment of the primary tumor? A SEER-based study. Eur Urol 65:1058–1066
26. Gratzke C, Engel J, Stief CG (2014) Role of radical prostatectomy in metastatic prostate cancer: data from the Munich Cancer Registry. Eur Urol 66:602–603
27. Heidenreich A, Pfister D, Porres D (2015) Cytoreductive radical prostatectomy in patients with prostate cancer and low volume skeletal metastases: results of a feasibility and case-control study. J Urol 193:832–838
28. Cho Y, Chang JS, Rha KH et al (2016) Does radiotherapy for the primary tumor benefit prostate cancer patients with distant metastasis at initial diagnosis? PLoS One 11:e0147191
29. Ost P, Reynders D, Decaestecker K et al (2018) Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence: a prospective, randomized, multicenter phase II trial. J Clin Oncol 36:446–453
30. Tree AC, Khoo VS, Eeles RA et al (2013) Stereotactic body radiotherapy for oligometastases. Lancet Oncol 14:e28–e37
31. Campbell PJ, Yachida S, Mudie LJ et al (2010) The patterns and dynamics of genomic instability in metastatic pancreatic cancer. Nature 467:1109–1113
32. Yachida S, Jones S, Bozic I et al (2010) Distant metastasis occurs late during the genetic evolution of pancreatic cancer. Nature 467:1114–1117
33. Gerlinger M, Rowan AJ, Horswell S et al (2012) Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. N Engl J Med 366:883–892
34. Wuttig D, Baier B, Fuessel S et al (2009) Gene signatures of pulmonary metastases of renal cell carcinoma reflect the disease-free interval and the number of metastases per patient. Int J Cancer 125:474–482
35. Pitroda SP, Khodarev NN, Huang L et al (2018) Integrated molecular subtyping defines a curable oligometastatic state in colorectal liver metastasis. Nat Commun 9:1793
36. Lussier YA, Khodarev NN, Regan K et al (2012) Oligo- and polymetastatic progression in lung metastasis(es) patients is associated with specific microRNAs. PLoS One 7:e50141
37. Wong AC, Watson SP, Pitroda SP et al (2016) Clinical and molecular markers of long-term survival after oligometastasis-directed stereotactic body radiotherapy (SBRT). Cancer 122:2242–2250
38. Uppal A, Ferguson MK, Posner MC et al (2014) Towards a molecular basis of oligometastatic disease: potential role of microRNAs. Clin Exp Metastasis 31:735–748
39. Zhang H-W, Wang E-W, Li L-X et al (2016) A regulatory loop involving miR-29c and Sp1 elevates the TGF-β1 mediated epithelial-to-mesenchymal transition in lung cancer. Oncotarget 7:85905–85916
40. Harazono Y, Muramatsu T, Endo H et al (2013) miR-655 Is an EMT-suppressive microRNA targeting ZEB1 and TGFBR2. PLoS One 8:e62757
41. Huang B, Luo W, Sun L et al (2013) MiRNA-125a-3p is a negative regulator of the RhoA-actomyosin pathway in A549 cells. Int J Oncol 42:1734–1742
42. Anaya-Ruiz M, Bandala C, Perez-Santos JLM (2013) miR-485 acts as a tumor suppressor by inhibiting cell growth and migration in breast carcinoma T47D cells. Asian Pac J Cancer Prev 14:3757–3760
43. Vaira V, Faversani A, Dohi T et al (2012) miR-296 regulation of a cell polarity-cell plasticity module controls tumor progression. Oncogene 31:27–38
44. Dykxhoorn DM, Wu Y, Xie H et al (2009) miR-200 enhances mouse breast cancer cell colonization to form distant metastases. PLoS One 4:e7181
45. Korpal M, Ell BJ, Buffa FM et al (2011) Direct targeting of Sec23a by miR-200 s influences cancer cell secretome and promotes metastatic colonization. Nat Med 17:1101–1108
46. Sapre N, Hong MKH, Macintyre G et al (2014) Curated microRNAs in urine and blood fail to validate as predictive biomarkers for high-risk prostate cancer. PLoS One 9:e91729
47. Hong MKH, Macintyre G, Wedge DC et al (2015) Tracking the origins and drivers of subclonal metastatic expansion in prostate cancer. Nat Commun 6:6605
48. Shah RB, Mehra R, Chinnaiyan AM et al (2004) Androgen-independent prostate cancer is a heterogeneous group of diseases: lessons from a rapid autopsy program. Cancer Res 64:9209–9216
49. Yuhas JM, Tarleton AE (1978) Dormancy and spontaneous recurrence of human breast cancer in vitro. Cancer Res 38:3584–3589
50. Braun S, Vogl FD, Naume B et al (2005) A pooled analysis of bone marrow micrometastasis in breast cancer. N Engl J Med 353:793–802
51. Kobayashi A, Okuda H, Xing F et al (2011) Bone morphogenetic protein 7 in dormancy and metastasis of prostate cancer stem-like cells in bone. J Exp Med 208(13):2641–2655
52. Zhou Y, Zhang G-J, Wang J et al (2017) Current status of lymph node micrometastasis in gastric cancer. Oncotarget 8:51963–51969