Acta Chirurgica Belgica

ISSN: 0001-5458 (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/tacb20

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To cite this article: Gilles Tilmans, Julie Navez, Mina Komuta, Thibaud Saussez & Jan Lerut (2020): Solitary prostate cancer liver metastasis: an exceptional indication for liver resection, Acta Chirurgica Belgica, DOI: 10.1080/00015458.2020.1722929

To link to this article: https://doi.org/10.1080/00015458.2020.1722929

Accepted author version posted online: 30 Jan 2020.
Published online: 11 Feb 2020.

ACTA CHIRURGICA BELGICA
https://doi.org/10.1080/00015458.2020.1722929

CASE REPORT

Solitary prostate cancer liver metastasis: an exceptional indication for liver resection

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ABSTRACT

Introduction: Prostatic cancer metastases (PCM) are usually systemic. Isolated PCM liver metastases (PCLM) are very rare. The treatment of PCM consists of hormono- and chemotherapy eventually combined with stereotactic radiation.

Patient and discussion: A case of a 67-year old man presenting with a solitary, metachronous PCLM undergoing a left extended hepatectomy due to resistance to hormono- and chemotherapy is reported. He died of recurrent systemic disease 31 months later.

Conclusions: The very rare indication and possible role of liver resection in the treatment of PCLM is discussed.

Abbreviations: LHRH: luteinizing hormone-releasing hormone analogue; MRI: magnetic resonance; PCM: prostatic cancer metastasis; PCLM: prostatic cancer liver metastasis; PC: prostatic cancer; PSA: prostate specific antigen; LHRH: Magnetic resonance imaging; IH: Immunohistochemistry; PAP: prostatic acid phosphatase; OS: overall survival; (PC) LM: (prostatic cancer) liver metastasis; PCOM: prostatic cancer osseous metastasis; NET: neuro-endocrine tumor; OM: oligometastatic; RFS: recurrence free survival; CRLM: colorectal liver metastasis; NETLM: neuro-endocrine liver metastasis; NCNNLM: non-colorectal non-neuroendocrine liver metastasis

ARTICLE HISTORY
Received 24 September 2019
Accepted 19 January 2020

KEYWORDS
Prostate cancer; liver metastasis; surgical resection; oligometastasis; hormonotherapy

Introduction

Prostate cancer (PC) is the first non-cutaneous malignancy and the second most common cause of death from cancer in men. Prostate cancer metastases (PCM), occurring in 35% of patients, are most common in bones, lungs and liver [1,2]. In case of visceral metastases the prognosis is poor [3]. The place of surgical resection is rare, the treatment of PCM merely consisting of combined hormono- and chemotherapy [4]. The case of a solitary, isolated metachronous, prostatic liver metastasis (PCLM) treated with liver resection is reported.

Case report

A 67-year old man underwent prostatectomy for prostate adenocarcinoma (PC) (Gleason unspecified, probably high risk PC) in 2004. His medical history included arterial hypertension and insulin independent diabetes mellitus. During follow-up determination of prostate specific antigen (PSA) and imaging were done regular. Eight years later a local (Gleason 8) recurrence was treated by radiotherapy and chemical castration using the luteinizing hormone-releasing hormone analogue (LHRH), gosereline acetate, (Zoladex®, AstraZeneca, Cambridge UK). Eighteen months later PSA level had increased from 0.04 to 32 ng/ml (nrl.value $<$0.04 ng/ml). PET-CT scan showed a hyper-metabolic lesion in both right colon and left liver. As the colonoscopy revealed a degenerated tubulo-villous adenoma the diagnosis of a metastazised colonic cancer was retained and a right hemicolectomy and liver biopsy were planned.

Surprisingly the pathology of the solitary liver lesion corresponded to PCLM. Magnetic resonance imaging (MRI) and a second PET-CT scan confirmed the solitary nature of a $59 \times 76 \times 52$ mm, large, centrally necrosed, tumor occupying liver segments II and IV and invading both left and median hepatic veins (Figures 1 and 2). Under Zoladex® therapy, PSA and testosterone levels lowered to 4.36 ng/ml and 0.097 nmol/L respectively.

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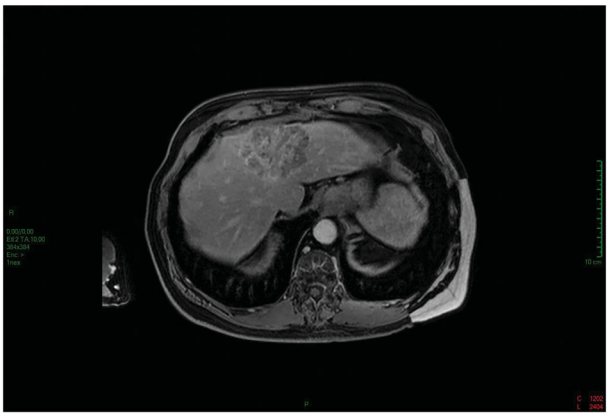

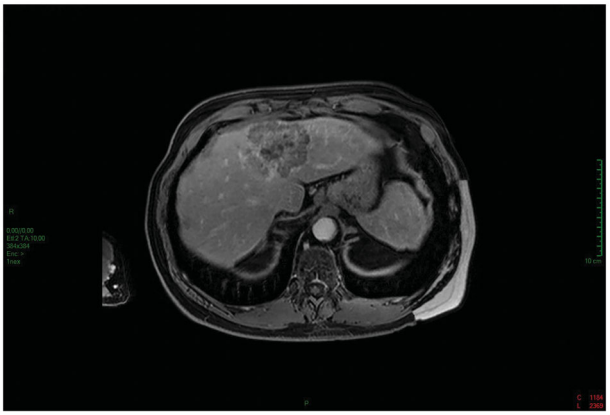

Figure 1 and Figure 2. Gadolinium *MRI* reveals a huge liver mass occupying liver segments II and IV presenting central necrosis, capsular retraction and invasion of left and middle hepatic veins.

After multidisciplinary tumor board discussion the hormonal therapy was reinforced by combining a monthly administration of the LHRH antagonist degarelix acetate (Firmagon®, Ferring SAS, Saint Prex CH) and 3-weekly administration of docetaxel (Taxotere®, Sanofi, B). After 6 cycles, PSA and testosterone levels further lowered to 1.47 ng/ml at 0.087 nmol/L, the size of the liver lesion decreased by 15% on imaging, but the vascular invasion remained unchanged. LDH value was normal at 176 U/L. Taking into account his excellent condition, as shown by a Karnofsky performance index of 90%, it was decided to resect this large isolated and solitary liver metastasis. After exploration of the abdominal cavity and confirmation of negative cytology, an extended left hepatectomy (segments II–IV and SVIII) was successfully performed. Pathology confirmed a R0 resection (13 mm margin) of a, 78 × 65 × 42 mm, large PCLM occupying liver segments II, IV and VIII. the non tumoral liver tissue was normal. The lesion was centrally necrosed and infiltrated the biliary tract, falciform ligament and left hepatic vein. Immunohistochemistry (IH) was positive for PSA and prostatic acid phosphatase (PAP) antigen in the cytoplasmic cells but negative for androgen receptor staining.

The postoperative course was complicated with a small biliary leak which required combined endoscopic and radiologic interventional treatment consisting of a sphincterotomy, biliary stenting and percutaneous drainage of a biloma. Two months post-surgery, PSA level normalized (<1 ng/ml). Hormonal therapy (Firmagon®) was continued. One year after surgery he developed pulmonary metastases followed later by (two) osseous lesions. Anti-androgen therapy using enzalutamide (Xtandi®, Astellas Pharma, Chuo-Ku Jp) was started and complemented some weeks later by cabazitaxel (Jevtana®, Sanofi Aventis, Fr). He died 31 months after liver surgery of generalized cancer spread.

Discussion

With an incidence rate of 214 per 1000 men, prostatic cancer is the most common solid cancer in men in Europe [5]. Although improved screening and management has significantly decrease the incidence of metastastic PC disease, 6.7% of individuals still present with metastases at diagnosis of their PC. Incidence and location of PCM vary widely.

In the literature the most frequent locations of PCM demonstrated by the usual screening methods are bones (90–91.1%), lungs (21–46%), supradiaphragmatic lymph nodes (8.7–34%), liver (4.5–37%), adrenal (13–15%) and brain (1.8%). Digestive tract, retroperitoneum, peritoneum and kidneys are less frequently involved [1,6,7]. According to the literature, the liver is the fourth most frequent metastatic site. Isolated LM without osseous or lymph node involvement is however, very rare.

Survival in case of PCM survival depends on site, number and type of metastases. The median overall survival (OS) rates in cases of visceral (commonly including the liver), osseous and lymph node metastases are 16 (range 12.9–19.1), 24 (range 22.9–25.1) and 43 (range 35.1–50.9) months respectively. In cases of combined localisations, OS decreases. In combined osseous and visceral PCM the OS rate is 14 months. Visceral metastases, with or without osseous metastases, carry the worst prognosis. The *number* of metastases is also important. In case of solitary metastasis OS rate reaches 24 months, in case of two or more metastases OS lowers to 15 months.

Table 1. Prognostic model for predicting survival in metastatic castration resistant prostate cancer: multivariable model predicting overall survival [8].

Factors	Parameters estimate	HR	95% CI	*p*
Performance status	0.392			<.0001
0		1.00	Referent	
1		1.48	1.31–1.67	
2		2.19	1.94–2.47	
Gleason score sum	0.335			<.0001
<8		1.00	Referent	
8–10		1.40	1.20–1.62	
Log (LDH)	0.312	1.37	1.21–1.55	<.0001
Log (Alkaline Phosphatase)	0.211	1.23	1.12–1.36	<.0001
Log (PSA)	0.093	1.10	1.05–1.15	<.0001
Visceral Disease	0.161			.147
No		1.00	Referent	
Yes		1.17	0.95–1.46	
Hemoglobin	−0.082	0.92	0.87–0.97	<.0001

Abbreviations: HR: Hazard ratio; CI: confidence interval; LDH: lactacte dehydrogenase; PSA: prostate specific antigen.

The mortality of patients presenting with visceral or combined visceral and osseous metastases is between 1.7- and 2-fold higher compared to patients with lymph node metastases [6]. PCLM is a bad prognostic factor and has therefore been included in Halabi's model predicting survival of hormone-refractory metastatic PC (Table 1) [8].

The *delay* between diagnosis of PC and PCLM is unclear from the literature. In the series of Pouessel et al. which includes 28 patients, the median time from initial diagnosis of PC to development of LM was 38 months. Six (21%) patients had LM as their first metastatic site; in just one (3.6%) the liver was the only metastatic site [2]. Biopsies of the liver lesions were positive for diagnosis of PCLM in four patients only; in two others the diagnosis of metastatic neuroendocrine tumor (NET) was made. The median OS from moment of appearance of LM was only 6 months (range 1 to 27) [2]. In the case reported here a single isolated PCLM was diagnosed ten years after initial PC diagnosis and two years after local recurrence.

Routine use of blood PSA level monitoring and of choline PET-CT scan, allows earlier diagnosis and more frequently isolated and oligo-metastatic disease (OM) [9,10]. According to the European Association of Urology-guidelines, LHRH agonists and androgen-deprivation-therapy are the standard treatment for metastatic PC [3]. The term OM, corresponding to a minimal metastatic state, has a distinct natural history as well as an intermediate prognosis between localized and widely spread metastatic disease. This concept is at the basis of the consideration of surgery, also termed "salvage metastasectomy", in the treatment of metastatic PC. The surgical treatment of a locoregional recurrence or a solitary metastasis mainly aims at postponing androgen-deprivation therapy, a treatment which not only has a limited efficacy but also is responsible for many side effects such as sexual dysfunction, physiologic and biologic osseous (osteoporosis and bone fractures) and body changes [3]. The Rigati et al. series which includes 72 patients, showed a significant benefit of 'salvage' pelvic lymphadenectomy (SLA) in patients presenting with PSA values < 4 ng/ml, (5-years recurrence free survival (RFS) of 48% vs. 11% in non-resected patient ($p = .004$) [11]. Other series identified PSA level at SLA, presence of LNM at time of radical prostatectomy, and pelvic LNM were associated with clinical relapse [12].

Resection of prostatic bone metastases (PCOM) also has been studied with a view to delaying androgen- deprivation therapy. Berkovic et al. showed in a prospective study of 24 patients that repeated stereotactic radiotherapy of PCOM allowed deferral of hormonal treatment by 38 months in cases of limited osseous or LN metastases [13]. In the series of Weiss et al. which included 306 patients presenting with single (7%) or multiple (73%) PCOM, surgical en-bloc resection resulted in a median survival of only 0.5 years (range 1–16) [14]. Similar results were reported by Ratasvuori et al. in a retrospective study of 146 PCOM patients [15]. Due to the heterogeneity of these studies it can only be concluded that stereotactic radiotherapy is the preferred treatment of PCOM based on its safety, low toxicity and high potential to delay progression [10]. Brain and lungs are uncommon sites of PCM. Isolated lung metastasis without LN involvement is rare. Due to lack of data, no conclusions can be made in relation to their prognosis and therapeutic strategy treatment [16].

Liver resection of colorectal (CRLM) or neuroendocrine (NETLM) liver metastases is nowadays a well established therapeutic option, allowing substantial prolongation of both OS and RFS rates and even, in well selected cases, to cure patients. Indications and prognoses of hepatectomy for non-colorectal, non- neuroendocrine liver metastases (NCRNNLM) still remain unclear due to the heterogeneity of primary diseases and the limited number of reported cases. The most common other primary tumor sites reported in case of surgical treatment of LM are breast, gastrointestinal and urologic tracts and melanoma [17]. In a retrospective analysis of 1452 patients with NCNNLM metastases from urologic primary tumors represent the third group ($n = 206$) following breast and

gastrointestinal primary tumors [16]. The median survival rate reached 51 months (range 36–82) and the 5 years OS was 48% (range 38–68%). In these large series no PCLM seemed to be included [17]. In the retrospective Arsis et al. study comprising170 patients undergoing liver resection for CRLM, OS was significantly better than for non-CRLM, (54vs.32 months, $p = .015$) [18]. Genitourinary (GU) cancers (7.6%) represented the second most frequent primary following colorectal (77.1%) and preceding neuroendocrine, breast, foregut and melanoma ones (77.1%, 5.3%, 4.7%, 2.9% and 2.4% respectively). OS after liver resection for GULM was 20% at 40 months.

A recent prospective study of 167 patients undergoing liver resection for NCRNNLM revealed that, compared to a matched CRLM population, OS and RFS were the best in the GU subgroup (45 vs.21 months for CRLM). OS after resection of renal cell cancer LM was comparable to resected CRLM (50 vs. 51 months) [4]. Ugerri et al. and Hoffmann et al., confirmed the encouraging results obtained after liver resection, done as a part of a multimodal treatment of GULM. Unfortunately, all these studies give no or very limited information about the type of primary GU tumor and do (very probably) not include any PCLM patient [4,18]. The lack of data in the literature about resection for PCLM can be explained by the very rare occurrence of isolated liver involvement in these patients [19,20].

The encouraging results obtained after liver resection for GULM should however raise the interest of the surgical community in the value of liver resection in case of PCLM. As prostatic cancer, in contrast to colorectal cancer, lacks a portal and splanchnic venous drainage, an isolated LM could be seen as a 'local disease', justifying surgical treatment in carefully selected cases [4]. Until new data are obtained, the evidence supporting the value of liver resection for PCLM remains very low. Accordingly an extensive literature search revealed only one such case reported by Kawai et al. These authors encountered a very similar case of liver resection for solitary PCLM occurring 15 years after radical prostatectomy which was also followed by a local reccurence one year later [21]. To the best of our knowledge the case presented here is the second reported in literature [21]. Our aggressive surgical approach was based on the singularity and very late presentation of the lesion, the excellent condition of the patient, the low PSA and testosterone levels and finally the stability of the liver lesion in the absence of further response to medical hormonotherapy. The reason for this hormonoresistance was clearly explained by the immunohistochemistry (IH) staining of the tumor revealing an absence of androgen receptors. Tumor biopsy including IH is of value because allowing to guide hormonotherapy as well as to exclude a possibly other (erroneous) diagnosis as observed by others, especially when such liver lesions appear late during the follow-up of prostatic cancer in elderly patients [2].

Conclusion

Isolated liver metastases from prostatic cancer are very rare. An unusual case of a chemically castration-resistant and a very delayed, solitary metachronous and isolated liver metastasis of a prostatic cancer is reported. An aggressive approach consisting of combined hormono- and chemotherapy and extended left liver hepatectomy was applied resulting in a 31 month survival. This case report shows that the place of liver surgery in the treatment of stable, single or oligometastatic prostatic cancer metastases should be further explored and that liver lesions, especially when appearing late during the follow-up of oncologic, in this case prostatic, patients, should be biopsied in order to refine the multimodal, medico-surgical, therapy.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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