The Clinical Relevance of Beta Blockers in Ovarian Carcinoma
A Systematic Review

Klinische Relevanz von β-Blockern beim Ovarialkarzinom
Ein systematischer Review

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Abstract

The last ten years have seen hardly any improvement in the prognosis of ovarian carcinoma. There is a great need for new treatment strategies, and a recent retrospective study showing a survival advantage with the use of beta blockers met with a very positive response. This systematic review summarizes the current state of knowledge and research on the topic: A database analysis identified six clinical studies showing inconsistent results with respect to the administration of beta blockers and disease course. The 13 preclinical studies identified showed almost without exception both that catecholamines had detrimental effects on tumour progression, and that these effects could be influenced by pharmacological blockade. Overall the available evidence does not justify the use of beta blockers in clinical practice for ovarian carcinoma at the present time. This article also outlines details of research design required for further studies needed on the subject. Preclinical research findings are however very impressive: They not only form an important basis for the development of future clinical studies but also, through revealing new pathomechanisms, they already make an important contribution towards the development of new treatment strategies for ovarian carcinoma.

Zusammenfassung

Die Prognose des Ovarialkarzinoms konnte in den letzten Jahrzehnten kaum verbessert werden. Der Wunsch nach neuen Therapiestrategien ist daher sehr groß und eine aktuelle retrospektive Studie zum Überlebensvorteil durch Einnahme von β-Blockern erzeugte große Resonanz. Diese systematische Übersicht soll den aktuellen Forschungsstand zum Thema zusammenfassen. In einer Datenbankrecherche konnten 6 klinische Arbeiten zusammengetragen werden, die in Bezug auf die Gabe von β-Blockern und den Krankheitsverlauf inkonsistente Ergebnisse zeigen. Die 13 gefundenen präklinischen Studien zeigen dagegen fast ausnahmslos ungünstige Einflüsse von Katecholaminen auf das Tumorgeschehen sowie die Möglichkeit der pharmakologischen Blockade dieser Einflüsse. In der Zusammenschau rechtfertigen die bisherigen Ergebnisse eine klinische Anwendung von β-Blockern beim Ovarialkarzinom zum jetzigen Zeitpunkt nicht. Es werden weitere Studien benötigt, deren Spezifika zum Forschungsdesign im Text erläutert werden. Die Ergebnisse der präklinischen Daten sind dagegen sehr eindrucksvoll und bilden nicht nur eine wichtige Basis für die Entwicklung zukünftiger klinischer Studien. Mit der Aufklärung neuer Pathomechanismen leisten sie bereits jetzt einen sehr wichtigen Beitrag bei der Arbeit an neuen Therapiestrategien gegen das Ovarialkarzinom.

Background

Ovarian carcinoma (OC) occupies seventh place on the list of female cancers in Germany [1]. Approximately 7500 women are diagnosed with the disease annually in Germany alone [1] and it is the fifth most common cause of cancer-related death among women [1]. This is partly due to the fact that OC is often diagnosed at an advanced stage. A large majority of cases (84%) are diagnosed at FIGO stage IIIC, i.e. the carcinoma has already spread beyond the pelvis and extrapelvic tumour size is larger than 2 cm [2,3].

Complete operative tumour resection has been identified as a decisive prognostic factor [4]. Systemic treatment with monoclonal antibodies such as bevacizumab (Avastin®) has been shown to prolong progression-free survival [5,6], how-

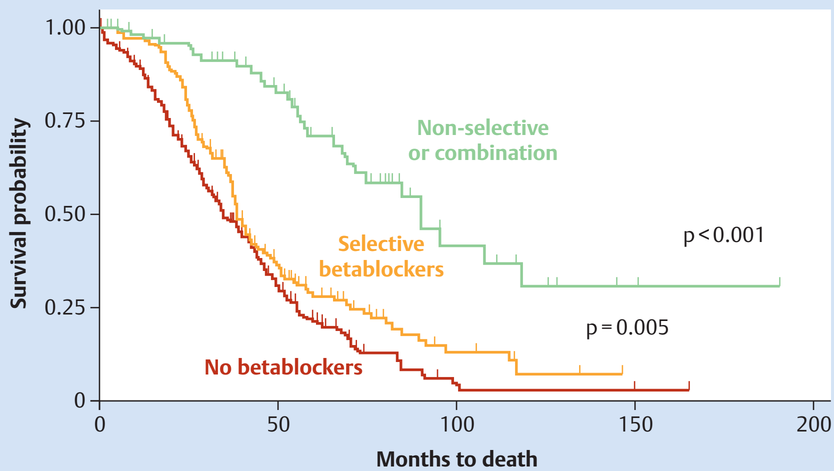

Fig. 1 Kaplan-Meier curve (overall survival) of patients with ovarian carcinoma treated with/without beta blockers. Median survival for patients without beta blockers was 34.2 months, with selective beta blockers 38.2 months ($p = 0.005$) and with non-selective beta blockers 90 months ($p < 0.001$) ([8], with kind permission).

ever actual survival advantage is not more than a few months [5, 6]. With a relative 5-year survival rate for all ovarian carcinomas of only around 42%, treatment results on the whole are unsatisfactory [1,7] and there is a dire need for new treatment concepts. A recent retrospective study showing a survival advantage for ovarian carcinoma patients treated with nonselective beta blockers met with a very positive response both in the lay and specialist press [8–10] (**Fig. 1**).

Contrary to the very optimistic, near sensational impression given by the lay press, numerous studies on the subject already exist [8, 11–15] whose findings have been critically appraised in the specialist literature [16]. All existing clinical studies are retrospective in nature, have heterogenous patient groups and to some extent present inconsistent results. The following article gives an overview of the latest preclinical data on the pathophysiology of catecholamines in ovarian carcinoma and summarizes the available clinical data on the use of beta blockers in this context.

Studies using animal model stress regimes and those focusing on psychological aspects, such as patient distress and the possible role of psychotherapeutic agents or psychiatric support, were excluded from this review due to capacity constraints. For a detailed discussion of these issues the reader is referred to an article by Hefner et al. [17]. Here we focus on pathophysiology at the biochemical level.

Basic Pathophysiologic Principles

Research on cell cultures and animal models from the past 15 years has consistently illustrated the detrimental effects of catecholamines on ovarian carcinoma and the possibility of blocking these effects. This is applicable to both the direct effects of catecholamines on tumour cells (anoikis, cell migration and invasion) [18–22] and indirect effects on the tumour microenvironment (inflammation, angiogenesis) [23–26] (**Table 1**).

Newly Discovered Pathomechanisms

The most recent preclinical studies on catecholamines in cancer provide deeper insight into some pathophysiologic interrelationships. In the context of ovarian carcinoma, studies of inflammation, cell senescence and chemoresistance have been particularly important. Propranolol, a nonselective beta blocker acting on both β1 and β2 adrenergic receptors has been used most in research (**Table 1**). In one study of inflammatory reactions the application of catecholamines to an ovarian carcinoma cell line lead not only to a rise in IL-6 and IL-8 but also to increased levels of monocyte chemotactic protein 1 (MCP1) [27]. MCP1 contributes to increased monocyte recruitment into tumour tissue, and raised MCP1 blood concentrations were associated with higher stage of disease, shorter progression-free survival and worse overall survival [27]. The catecholamine induced rise in IL-6, IL-8 and MCP1 concentrations observed in the cell line was inhibited by beta blockers [27] (**Table 1**).

Another study discovered a previously unknown interconnection between the signal pathways of catecholamine and prostaglandin metabolism [28]. In the experiment by Nagaraja et al. noradrenaline application lead to increased PGE2 production via the ADRB2–NF-κB–PTGS2–PGE2 signal cascade in cell lines with β adrenergic receptors, and to increased activity of the PTGS2 and PTGES genes necessary for this to occur [28]. In an orthotopic mouse model experimental deactivation of the PTGS2 gene lead to reduced tumour load and metastasis [28]. A genome analysis of patients found that strong expression of β2 adrenergic receptors, PTGS2 and PTGES was associated with reduced progression-free survival and overall survival [28] (**Table 1**).

Another previously unknown pathomechanism was discovered during studies of telomerase. In up to 95% of ovarian carcinoma cells the catalytic subunit of telomerase (hTERT) is upregulated in order to stabilise tumour cell telomeres [29, 30]. A complex signal pathway to hTERT via β2 adrenergic receptors/PKA/Src/HIF-1α/c-Myc was demonstrated on addition of noradrenaline to ovarian carcinoma cells. Simultaneously, hTERT induced the expression of Slug, a central gene in epithelial-mesenchymal transition [EMT]) [31] (**Table 1**). EMT itself is regarded as essential for the development of newly discovered ovarian carcinoma cancer stem cells of [32, 33]. In a study by Choi et al. using a mouse model noradrenaline administration lead to increased hTERT expression and pulmonary metastasis of ovarian carcinoma cells [31] (**Table 1**).

Studies on chemoresistance in association with catecholamines have proven to be particularly significant with respect to clinical disease course. It is already known from preclinical studies on other tumour entities that catecholamines increase chemoresist-

Table 1 Preclinical studies: effects of agonists and antagonists on adrenoreceptors in ovarian carcinoma.

Author, year published	C/X	Agonist	Effect	Effect blockade	No blockade
Sood 2010 [18]	C	A, N	Reduced anoikis (by a factor of 0.5)	Propranolol	
Rangarajan 2003 [19]	C	I	Increased cell adhesion (factor: 1.5)		
Enserink 2004 [20]	C	I	Increased cell migration (factor: 3)		
Sood 2006 [21]	C	A, N N N	Increased propensity to invade (198 %) Raised MMP-2 concentration Raised MMP-9 concentration		
Landen 2007 [22]		A, N	Raised STAT3-concentration Increased propensity to invade (factor: 3.1) Raised MMP-2 concentration Raised MMP-9 concentration	Propranolol	Prazosin Yohimbine
Nilsson, 2007 [23]	C X	A, N, I I	Increased IL-6 secretion (by a factor of 200) Increased tumour mass (factor: 5)	Propranolol	
Shazad 2010 [24]	C	A, N	Increased IL-8 secretion (factor: 3) Increased IL-8 mRNA transcription (factor: 3.2) Increased IL-8 promoter activity (factor: 4)	Propranolol	
Lutgendorf 2003 [25]	C	A, N, I	Increased VEGF production	Propranolol	
Thaker 2006 [26]	C	N, I	Increased VEGF mRNA transcription (factor: 8.4) Increased VEGF mRNA promoter activity (factor: 12.4)	Propranolol	
	X	I, T	Increased tumour mass (factor: 2.5)	Propranolol	
Armaiz-Pena 2015 [27]	C	A, N, I	Raised IL-8, IL-8, VEGF, MCP1 levels	Propranolol ICI118.551	Atenolol SR59230A
Nagaraja 2015 [28]	C	N, I, T	Raised PGE concentration Increased PTGS2 expression (factor: 4) Increased PTGES expression (factor: 28)	Propranolol Butoxamine	
	C	N	Increased p65 and p50 in cell nuclei Increased NF-κB binding to PTGS2 and PTGES		
	X	N	Increased number of tumours Increased tumour size		
Choi 2015 [31]	C	N	Increased hTERT expression		
	X	N	Increased propensity to metastasise		
Kang 2015 [36]	C	N, I before paclitaxel or cisplatin	Reduced apoptosis rate (43 %) Increased DUSP1 expression Increased DUSP mRNA transcription	Propranolol ICI118.551 SR59230A (partially)	Atenolol
	C	N, I, T	Increased DUSP1 promoter activity	Propranolol ICI118.551	Metoprolol SR59230A

C = cell culture, X = xenograft
A = adrenaline = nonselective β agonist, N = noradrenaline = nonselective β agonist, I = isoproterenol = nonselective β agonist, T = terbutaline = β2 agonist, propranolol = nonselective β blocker, atenolol = β1 blocker, butoxamine = β2 blocker, ICI118.551 = β2 blocker, SR59230A = β3 blocker, prazosin = α blocker, yohimbine = α2 blocker

ance of tumour cells and that beta blockers can potentiate chemotherapeutic effects [34,35]. The most recent work on ovarian carcinoma now shows similar results [36]. Various cell lines were treated with catecholamines and thereafter exposed to paclitaxel or cisplatin. The apoptosis rate usually observed under these chemotherapeutic agents was reduced [36]. The effect was only demonstrable on application of substances with β2 receptor agonist properties, and only in cell lines possessing β2 receptors [36]. This disadvantageous effect on chemotherapeutic action was mediated by the dual specificity phosphatase 1 (DUSP1), whose expression was increased by the stress hormones [36]. In addition a further signal pathway was described that mediates JNK-dependent phosphorylation of c-Jun via cAMP-PLC-PKC-CREB, protecting ovarian carcinoma cells from apoptosis [36]. There was no loss of chemotherapeutic effect after application of a β2 receptor blocker [36] (**Table 1**).

Beta Blockers and the Clinical Course of Ovarian Carcinoma

Negative or inconsistent results

First abstracts on the clinical application of beta blockers in ovarian carcinoma were published in 2012 by Eskander et al. [11,12]. In a retrospective, single centre study of overall survival no survival advantage was shown for the use of beta blockers in a study population of 680 newly diagnosed patients from all disease stages [11]. Prolonged beta blocker use for more than 2.5 years was associated with a 47 % reduced likelihood of dying from ovarian carcinoma. Overall and progression-free survival were determined retrospectively using 489 data sets from the same patient collective [12]. Here the analysis showed significantly reduced survival with beta blocker use, especially among younger patients (< 61 years); there was a nonsignificant negative trend for progression-free survival with beta blocker use [12] (**Table 2**). Johannesdottir et al. performed a far more extensive, retrospective analysis of 6626 data sets from the Danish Cancer Registry of newly diagnosed ovarian carcinoma patients at all stages of

Table 2 Clinical studies on beta blockers and disease course in ovarian carcinoma (OC).

Author, year, design	Tumour entity, n	Type of beta blocker	Duration of use (UD)	Results with/without beta blocker Hazard ratio (HR)
Eskander 2012 [11] Retrospective Single centre	Initial diagnosis Epithelial OC Stage I–IV Total n = 680 With beta blocker n = 144	Undefined	UD > 30 d prior to diagnosis UD ≥ 2.5 years	Overall survival 23 vs. 20 months (n. s.) HR death due to OC = 0.53 (n. s.)
Eskander 2012 [12] Retrospective Single centre	Initial diagnosis Epithelial OC Stage Ic – IV Total n = 489 With beta blocker n = 107	Undefined	UD > 30 d prior to diagnosis UD > 30 d prior to diagnosis	Overall survival 26.7 vs. 30.5 months (p = 0.015) Progression-free survival 19.3 vs. 21.3 mo. (n. s.)
Johannesdottir 2013 [13] Retrospective Cancer registry	Initial diagnosis OC Total n = 6 626 With beta blocker n = 460	Undefined	 UD = most recently < 90 d prior to diagnosis UD = most recently > 90 d prior to diagnosis	Compared to no beta blocker HR for death = 1.17 (n. s.) HR for death = 1.18 (n. s.)
Heitz 2013 [14] Retrospective Analysis of AGO studies Ovar 2.4 and 2.5	Recurrence Platinum sensitive OC Total n = 381 With beta blocker n = 38	Sel. β1 blocker n = 32 Non-sel. beta blocker n = 6	Undefined	Overall survival 21.2 vs. 17.3 months (n. s.) Progression-free survival 7.79 vs. 7.62 months (n. s.)
Diaz 2012 [15] Retrospective Single centre	Initial diagnosis Epithelial OC Stage III–IV Total n = 248 With beta blocker n = 23	Sel. β1 blocker n = 17 α/β-receptor blocker n = 3 Non-sel. beta blocker n = 3	Undefined	OC specific survival 56 vs. 34 months (p = 0.02) Progression-free survival 27 vs. 17 months (p = 0.05)
Watkins 2015 [8] Retrospective Multicentre	First diagnosis Epithelial OC All stages > 1 chemotherapy cycle Total n = 1 425 With beta blocker n = 269	Sel. beta blocker n = 194 Non-sel. beta blocker n = 75	 UD ≥ 1 year UD ≥ 5 years	Overall survival 47.8 vs. 42 months (p = 0.036) 38 vs. 94.9 months (p < 0.001) Compared to no beta blocker Overall survival HR = 0.26* OC specific survival HR = 0.24** Overall survival HR = 0.62† OC specific survival HR = 0.63‡

AGO = study group of the working group for gynaecological oncology of the German Society of Obstetrics and Gynaecology
n. s. = non significant
* 95 % CI: 0.19–0.37; p < 0.0001, ** 95 % CI: 0.17–0.34; p < 0.0001, † 95 % CI: 0.47–0.81; p < 0.0005, ‡ 95 % CI: 0.48–0.83; p = 0.001

disease. Disease course was compared between patients who had never taken beta blockers, those who had used beta blockers less than 90 days prior to data acquisition, and those who had used them more than 90 days previously [13]. There was no difference in mortality risk between the groups [13] (**Table 2**).
In the context of recurrent ovarian carcinoma, Heitz et al. found no advantage for the use of β1 receptor blockers in a retrospective analysis of the prospective, multicentre Ovar-2.4 and Ovar-2.5 studies that were initiated by the working group for gynaecological oncology (AGO) of the German Society of Obstetrics and Gynaecology [14, 37, 38] (**Table 2**).

Positive results

Diaz et al. reported a statistically significant benefit for both disease-specific and progression-free survival at disease stages III and IV with the use of beta blockers [15]. In their retrospective, single centre study the authors calculated that beta blockers lead to a 54 % reduced chance of dying [15] (**Table 2**).
Recently the much discussed retrospective, multicentre study by Watkins et al. including 1425 ovarian carcinoma patients at all stages of disease also showed a survival advantage for the use of beta blockers [8] and a distinction between selective and nonselective beta blockers was documented for the first time [8]. Although use of selective beta blockers produced a survival advantage overall, median survival was significantly worse (38.2 months) than with nonselective beta blockers, and in some cases the use of selective beta blockers was even associated with reduced survival [8]. In contrast, median survival using nonselective beta blockers was 90 months compared to 34.2 months in patients not receiving any beta blocker [8]. The hazard ratio (HR) for death following a diagnosis of ovarian carcinoma was 0.26 with beta blockers overall, 0.32 for selective beta blockers and 0.08 for nonselective beta blockers [8] (**Table 2**).

Discussion

Ovarian carcinoma remains one of the most commonly occurring, and one of the most commonly fatal malignancies in women [1]. Treatment options developed over the past 50 years have not improved disease prognosis significantly [1, 7] and innovative treatment alternatives are urgently needed.
In the realm of preclinical research impressive studies of first-rate quality have been published for most of the hallmarks of cancer [39].

These include studies on chemoresistance, invasivity, migration and adhesion tendency, inflammation reactions and angiogenesis [18–21,23–27,36,40]. Recent discoveries such as interconnections between the metabolism of catecholamines and pain mediators [28], or EMT and cancer stem cell development [31] provide new targets for potentially innovative treatments (▶ **Table 1**).

Despite these successes at the pathophysiological level many questions remain open, such as the significance of the autonomic innervation of tumour tissue [41], the roll of β3 receptors [42] and apoptosis pathways via protein p53 [41]. The sporadically observed positive effects of catecholamines and negative effects of beta blockers remain completely unexplained and require urgent further study [40].

Important points of criticism of the preclinical work to date include the use of pharmacological doses of catecholamines and xenografts, both of which complicate the assessment of clinical significance. However this applies to preclinical research on ovarian carcinoma in general, which requires innovative studies of pathomechanisms using modified cell lines and animal models [43]. These studies could be usefully expanded on through studies of catecholamines and beta blockers. As an example, on the basis of experience with MCP1, the combination of checkpoint inhibitors and beta blockers could constitute an innovative design to enable the study of immune therapy synergism [27,44, 45].

Despite the limitations and justified criticism of this preclinical data it has nevertheless convinced many researchers that catecholamines do promote relevant aspects of tumour progression, and that especially nonselective beta blockers could reduce these effects [46].

And indeed the latest clinical work on the influence of beta blockers not only on ovarian carcinoma but also on breast cancer and malignant melanoma, does prima facie support this conclusion [8–10,46–53]. In a recent multicentre study including 1425 patients with ovarian carcinoma at all different stages, on retrospective analysis beta blockers were shown to provide a significant survival advantage [8], and for the first time, an advantage of nonselective beta blockers over selective beta blockers was demonstrated [8]. This result fulfills the hypothesis of preclinical studies where the main beta blocker effect was shown to occur via β2 receptors [36,41,42]. At the same time it provides a possible explanation for the nonsignificant findings of studies that either did not stratify by β receptor type [11–13] or in which patients mainly took β1 receptor blockers [14]; the findings of Diaz et al. are in disagreement though, showing a survival advantage for beta blocker use even though the majority of their patients took β1 receptor blockers [15] (▶ **Table 2**). The most controversial issues, however, surround prognosis. Diaz et al. found survival advantages for patients in the more advanced disease stages III and IV in particular, and in the study by Watkins the hazard ratio for death for patients at all disease stages following diagnosis of ovarian carcinoma was 0.26 for those taking beta blockers, 0.32 for selective beta blockers, and 0.08 for nonselective beta blockers [8]. In stark contrast, the HR for the use of platinum-based chemotherapy in advanced disease was calculated at 0.88 [54]. If true, this would make beta blockers a sort of "wonder drug", their effects far surpassing those of standard treatments [16]. This is seriously doubted by commentators [16] however, who suspect the results may have been skewed by a statistical bias (so-called "immortal person-time bias") [16]. This occurs when the definition of an exposure or a covariable is dependent on an event (e.g. starting beta blocker treatment) occurring after the start of the follow-up period; in the time between the beginning of follow-up and e.g. starting a beta blocker the patient is statistically "immortal" and their data will distort the group's survival time [16]. Watkins and his co-authors dispelled this criticism in their case stating that only an estimated 5% of study participants had started beta blockers after the beginning of follow-up [55]. In addition they referred to preclinical studies on ovarian carcinoma and other tumour entities where beta blockers helped to sensitise malignant cells to chemotherapeutic agents, potentiating chemotherapy effects [34–36,56,57]. Initial groundbreaking prospective clinical work on pancreas carcinoma has shown nearly doubled survival rates with the addition of a combination of beta blockers and COX-2 inhibitors to standard chemotherapy [58].

Despite the euphoria, however, it should not be forgotten that all clinical studies on ovarian carcinoma to date have been retrospective in nature, and at best should be considered as contributing towards the generation of hypotheses. In view of the poor prognosis associated with ovarian carcinoma it is very possible that a publication bias/"file drawer problem" exists, where nonsignificant or negative results are not published, and that positive findings even from retrospective studies receive undue acclaim both in the speciality and lay press [59,60]. In addition, further distortion of results due to the previously mentioned "immortal person-time bias" must be assumed, since, according to a recent review, all positive effects of beta blockers in cancer are subject to this bias [61]. Further limitations of the reviewed studies of ovarian carcinoma are their retrospective nature, limited patient numbers and the fact that the various disease stages were not considered separately. No study has yet considered the beneficial effects of catecholamines in the context of peritoneal carcinomatosis and severe tumour recurrence, or the possibility of perioperative beta blockade [62–64]. Before beta blockers can be widely implemented in clinical practice for ovarian carcinoma a "second wave" of clinical studies is required [65] that are at least prospective in design with a focus on relevant biomarkers [66]. As is also the case with other tumour entities it will be necessary to study the receptor profile and density in ovarian carcinoma in order to select suitable beta blockers [41]. The expression profiles of catecholamine dependent genes before application of beta blockers have also not yet been determined [41]. Most importantly, however, when selecting a beta blocker increased attention must be paid to the individual patient's comorbidities and relevant drug indication restrictions and side effect profiles. Although beta blockers in general are known to be safe and economic from decades of use in other areas of medicine, selective beta blockers, which have been preferred in other medical fields in view of their favourable side effect profile, appear to be less effective in ovarian carcinoma and may even be detrimental [8,14]. Also, without in-depth knowledge of possible drug interactions beta blockers used as co-medication with standard chemotherapies increase the risk of side effects. Pharmacokinetic characteristics should also be investigated in vivo since beta blocker degradation via the cytochrome system is well known and could contribute to increased excretion with consequent reduced efficacy on an individual basis [8]. Lastly, the consideration of specific time points in the disease course may prove innovative: preclinical data suggest so-called "windows of opportunity" (e.g. during chemotherapy or when metastasis or recurrence occur) during which beta blockers may be particularly effective [41,42,47]. To our knowledge, both a feasibility study and a prospective study on the clinical application of beta blockers in ovarian carcinoma are currently underway [67,68]; we eagerly await their results as they may provide first data justifying the use of beta blockers in ovarian carcinoma.

Conclusion

Preclinical data clearly indicate that catecholamines influence ovarian carcinoma unfavourably. In vitro these catecholamine effects can be inhibited with the aid of beta blockers. Recent studies also report benefits from beta blockers in clinical practice, however these optimistic reports are based on retrospective data analyses. Existing studies assist the generation of new hypotheses, e.g. on pathophysiologic interrelationships, and form a basis for future prospective clinical studies with a focus on relevant biomarkers. The evidence published to date, however, does not justify the widespread clinical application of beta blockers in ovarian carcinoma.

Conflict of Interest

The authors declare that no conflict of interest exists.

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