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Comparative evaluation of three palliative external beam radiotherapy schedules in painful bone metastases

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ORIGINAL ARTICLE

Comparative evaluation of three palliative external beam radiotherapy schedules in painful bone metastases

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Abstract

Background: *Bone metastases are a common manifestation of many malignancies. External beam radiotherapy (EBRT) provides successful palliation of painful bone metastases. In the present study, we compared three schedules of palliative EBRT in painful bony metastasis.* **Objective:** *To evaluate pain relief and performance status improvement in these patients.* **Method:** *This prospective, study was conducted on patients of painful bone metastases from any primary. Patients were randomly divided into three groups to received palliative EBRT either 6Gy single-session (group-I), or 8Gy single-session (group-II) or 10Gy/2-fractions/1-week apart (group-III) to the involved site. Primary objective was to assess overall pain response, assessed using Glasgow pain scale and improvement in performance status, assessed using Eastern Cooperative Oncology Group (ECOG) performance status score. Secondary objectives measured were complete pain relief, duration of overall pain response, analgesic requirement and need of re-irradiation.* **Results:** *A total of 60-patients were equally randomized into 3 groups.* **Conclusion:** *Pain relief was observed maximum in group-III. In all three groups, mean baseline pain score was significantly reduced, and mean ECOG performance status improve 1-month post-EBRT.*

Keywords: *Bone metastasis. External beam radiotherapy. Painful. Palliation. Single session.*

Evaluación comparativa de tres programas paliativos de radioterapia de haz externo en metástasis óseas dolorosas

Resumen

Antecedentes: *Las metástasis óseas son una manifestación común de muchas neoplasias malignas. La radioterapia de haz externo (EBRT) proporciona una paliación exitosa de las metástasis óseas dolorosas. En el presente estudio, comparamos tres esquemas de EBRT paliativo en metástasis óseas dolorosas. Objetivo: Evaluar el alivio del dolor y la mejora del estado funcional en estos pacientes.* **Método:** *Este estudio prospectivo se realizó en pacientes con metástasis óseas dolorosas de cualquier primario. Los pacientes se dividieron aleatoriamente en tres grupos para recibir EBRT paliativa, ya sea 6Gy en una sola sesión (grupo I), 8Gy en una sola sesión (grupo II) o 10 Gy/2 fracciones/1 semana de diferencia (grupo III) hasta el sitio involucrado. El objetivo principal fue valorar la respuesta general al dolor, evaluada mediante la escala de dolor de Glasgow y la mejora en el estado funcional, mediante la puntuación del estado funcional del Eastern Cooperative Oncology Group (ECOG). Los objetivos secundarios medidos fueron el alivio completo del dolor, la duración de la respuesta general al dolor, la necesidad de analgésicos y reirradiación.* **Resultados:** *Un total de 60 pacientes fueron igualmente asignados al azar en 3 grupos.* **Conclusión:** *El alivio del dolor se observó máximo en el grupo III. En los tres grupos, la puntuación media inicial del dolor se redujo significativamente y el estado funcional ECOG medio mejoró 1 mes después de la EBRT.*

Palabras clave: *Metástasis ósea. Radioterapia de haz externo. Doloroso. Paliación. Sesión única.*

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Introduction

Development of distant metastasis is seen with progression of cancer, and once distant spread occurs, the disease becomes more advanced, mostly incurable, and fatal[1]. Among different organs involved by metastatic cancer cells, bone seems to be third in order, only after lung and liver[2,3]. The frequent primary malignancies those usually cause bone involvement as distant spread are breast, prostate, lung, kidney, and multiple myeloma[1,3,4]. Bone metastasis can be osteoblastic or osteolytic or mixed type, depending on the interaction between circulating cancer cells and bone formation mechanism[5]. Osteoblastic deposits are predominantly seen in prostate cancer; osteolytic lesions mainly occur in multiple myeloma, renal cell carcinoma, and mixed type lesion can be seen in primary breast cancer, gastrointestinal malignancies, and so on[6]. Long-term and diffuse, multiple bone involvement by secondary deposits leads to a few typical sign and symptoms, collectively known as skeletal related-event (SRE)[4,7]. These can be pathological fracture, compression of spinal cord, impairment in movement, bone marrow depression leading to anemia or pancytopenia, hypercalcemia, and most importantly severe, refractory pain[4,6,7]. Majority of patients having bone metastasis presented with chief complain of severe bone pain not relieving by routine analgesics and thus having decreased daily performance and poor quality of life (QoL)[8].

The appearance of bone metastasis in any malignancy denotes poor prognosis and in most of the cases, the treatment intent becomes palliation[9,10]. The treatment of bone metastasis includes an inter-disciplinary multimodality effort with contributions from various fields such as involvement of orthopedic surgeon, radiation and medical oncologists, nuclear medicine specialists, interventional radiologists, pain specialist, and often neurovascular surgeons[9]. Therapeutic strategy includes but not limited to external beam radiotherapy (EBRT), systemic therapy consisting of chemotherapy, targeted agents and hormonal drugs, targeted radionuclide therapy, surgical and orthopedic intervention, and associated conservative therapies with bone-targeted agents such as bisphosphonates and receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors[4,8]. EBRT provides dramatic relief in localized metastatic bone pain and is considered the reference treatment in palliation of pain and other SRE caused by bone metastasis[6]. After EBRT, rapid pain relief usually occurs in majority of the patients with more than 50% of patients had complete pain relief[6,11]. Historically, multifractional dose-schedules were considered appropriate for palliation of bone metastasis[10,12]. However, a few analyses, in different parts of world, comparing single versus multifraction have concluded that single fraction dose-schedule is as effective as traditional multifraction regimen[13-17]. The same has been assessed in this study in bone metastasis patients of Indian origin. The purpose of this study was to compare three schedules of palliative radiotherapy (6 Gy single session [SS], 8 Gy SS, and 10 Gy in 2 fractions, 1 week apart) with respect to pain-relieving and functional status improving in patients of painful bone metastases from any primary.

Materials and methods

This is a prospective and randomized study, which was conducted on patients of painful bone metastases from any solid tumor primary. Bone metastasis was confirmed by either histopathology (biopsy or cytology) or by modern imaging technique (magnetic resonance imaging, bone scintigraphy or positron emission tomography). All the patients had histopathological proven primary malignancy and most of them received treatment for primary earlier. The pre-treatment evaluation was done in all patients which included complete history, general physical, and systemic examination. The assessment of the patient's functional outcome was done by Eastern Cooperative Oncology Group (ECOG) performance status score. The pain score in each patient was calculated using the Glasgow pain scale. Based on the initial evaluation, those patients were considered eligible for the study, who were having ≥ 18 years of age, pain intensity on a numeric rating scale of 4-10, and were ready for palliative EBRT to metastatic site(s). Those patients were excluded from the study, who had been treated before with radiotherapy to the concerned region and patients having any serious comorbid conditions to which the patient's symptoms could be attributed. Patients having single-site bone metastasis, with controlled primary and could be taken for curative treatment were also excluded from the study.

The study was conducted after getting informed consent from all the enrolled patient and approval of the institutional review board. All the enrolled patients were randomly divided into three groups equally with the help of computer-generated randomization. In all three groups, all the patients received palliative EBRT to involved site (single or multiple bones). Patients were given 6 Gy SS, 8 Gy SS, and 10 Gy in two fractions (5 Gy/fraction, 1 week apart) in Group I, II, and III, respectively. EBRT was given on megavoltage cobalt-60

teletherapy machines in 2-dimensional conventional technique, taking appropriate margin as per standard guidelines. Treatment position was prone or supine depending on the involved bone(s) and treatment technique. EBRT was combined with associated conservative treatment as needed. Radiation therapy to primary site and systemic therapy, that is, chemotherapy and targeted agents (intravenous or oral metronomic) were administered to patients as indicated, to reduce the primary and metastatic disease burden. Repeat palliative radiation to the same site was offered if pain did not subside significantly, a minimum of 3 months after first radiation. Patients were followed up after radiotherapy for a total period of 6 months, that is, bi-weekly for 1 month, and then monthly for 5 months. At each follow-up, patients were assessed for pain palliation using the Glasgow pain scale and functional outcome using the ECOG score.

Primary objectives were to assess overall pain response and improvement in functional or performance status. Secondary objectives measured were complete pain relief, duration of overall pain response, analgesic requirement, and need of reirradiation. Overall pain response was defined as decrease in pain score by at least two points with respect to the pre-treatment value. Improvement in performance status was defined as a decrease in ECOG score by at least one grade with respect to pre-treatment value. Complete pain response was defined as achieving a pain score of 0 at any point during follow-up. Duration of overall pain response was defined as time from initial response till return of pain to its baseline value.

The data thus received were entered in Microsoft Excel (version 2019) and analyzed with Statistical Package for the Social Sciences software version 26.0. Patient characteristics were summarized using descriptive statistics. Quantitative data were presented as mean and standard deviation, while qualitative data were presented as ratios and proportions. A comparison of quantitative data was done by analysis of variance test after confirming the normality of the data. Chi-square test and Fisher's exact test were used for qualitative data whenever two or more than two groups were used to compare. The level of statistical significance was set as $p < 0.05$.

Results

Over a period of 1 year, a total of 60 patients, fulfilling inclusion criteria, were enrolled in this study, after getting informed consent and were equally randomized into three groups as mentioned earlier, that is, each group having 20 patients each. Details of patients' characteristics were depicted in tabulated format (Table 1) and there was no significant difference among the three groups. The mean and median age of presentation was 56.9 years and 60 years, respectively; the range was from 27 to 85 years (Fig. 1). Baseline tumor profiles, both primary and metastatic, were also illustrated in table 2. Tumor characteristics appeared to be well-balanced among the study groups, with the majority of patients having lung cancer as primary lesion.

Post-treatment observation for primary and secondary endpoints in all three groups was depicted in tabulated format (Table 3). Maximum patients got pain relief at 4th week (1 month) post-radiotherapy, and all patients had sustained pain relief, that is, pain score less than pre-treatment pain score anytime during 6th month of follow-up. The mean baseline pain score was significantly reduced after 4th week of post-radiotherapy in all three groups (Fig. 2). From the 4th week (1 month) to 4 months, almost a similar mean pain score was observed. From the 5th month follow-up, there was an increase in mean pain score in each group but never equal to or above pre-treatment values. Mean ECOG performance status was improved after radiation therapy in all three groups (Fig. 3). Most patients of all three groups had decrease analgesic requirement at 1-month follow-up. Furthermore, a downward shift in analgesic uses, that is, from use of opioids to non-opioid, simple non-steroidal-anti-inflammatory-drugs (NSAIDs), was also noticed in all the groups. However, an increasing trend of analgesic requirement was observed 5th month follow-up onward, and this was true for all three groups.

Discussion

Bone is very common sites for secondary deposits in advanced solid tumor. Most of the time, skeletal metastasis is seen in multiple bones[6]. Pain is the most common presenting symptoms in patients having bone metastasis. It may be localized or diffuse, progressive with time, and often worsen with daily routine activities; at first relived by conventional analgesics, that is, NSAIDs; but later opioids and other modalities of management are needed for pain relief[18]. Efficacy of bone-targeted agents such as bisphosphonates (zoledronate, ibandronate, pamidronate etc.), RANKL inhibitor (denosumab) in bone metastasis by reducing pain, decreasing fractures incidence, and less chance of developing new skeletal lesions and thus improve the QoL is well established[19,20]. Howbeit, in practical situation many patients did not get the expected benefits from this treatment;

Table 1. Baseline patients characteristics of bone metastasis patients in all three groups

Characteristics	Group I (%)	Group II (%)	Group III (%)
Mean age (in years)	59.50	58.25	53.55
Gender	M: 11 (55)	M: 08 (40)	M: 11 (55)
	F: 09 (45)	F: 12 (60)	F: 09 (45)
Background	R: 16 (80)	R: 14 (70)	R: 15 (75)
	U: 04 (20)	U: 06 (30)	U: 05 (25)
Smokers	Y: 11 (55)	Y: 10 (50)	Y: 08 (40)
	N: 09 (45)	N: 10 (50)	N: 12 (60)
Alcoholic	Y: 09 (45)	Y: 08 (40)	Y: 07 (35)
	n: 11 (55)	n: 12 (60)	n: 13 (65)
ECOG	Score ≤ 2: 09 (45)	Score ≤ 2: 12 (60)	Score ≤ 2: 07 (35)
	Score > 2: 11 (55)	Score > 2: 08 (40)	Score > 2: 13 (65)
Glasgow Pain Scale	Moderate (4-6): 06 (30)	Moderate (4-6): 04 (20)	Moderate (4-6): 03 (15)
	Severe (7-10): 14 (70)	Severe (7-10): 16 (80)	Severe (7-10): 17 (85)

ECOG: Eastern Cooperative Oncology Group; F: Female; M: Male; N: No; R: Rural; U: Urban; Y: Yes.

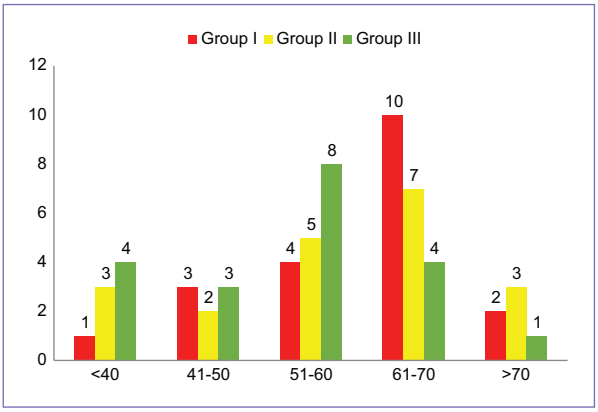

Figure 1. Age-wise distribution of bone metastasis patients in all the three groups.

thus, to prevent further disease progression and also for more palliation benefit additional treatments for bone metastasis needed[21]. Radiotherapy, both EBRT and radionuclides, can be used in the management of analgesic-refractory pain arising from skeletal metastasis[18,22]. Local site EBRT, using either small-to-medium field radiation or large-field like hemibody irradiation, is established treatment for palliation of bone metastasis[22-24]. Conventionally, 30Gy in 10 fractions was the most widely used dose-fractionation schedules in achieving palliation of these patients[10,12,23]. However, various other dose fractionations were widely explored and used as routine practice globally (Table 4)[13-17,25-27]. Two large-scale meta-analyses also confirmed the pain-relieving efficacy of different single dose-fractionation schedules[28,29]. Practice of single fraction RT was also increased during the COVID pandemic as it decreased number of hospital visit without hampering effective pain control[30].

Our analysis revealed an equal incidence of bone metastasis among male and female. In general, gender-wise incidence of bone metastasis depends on the primary tumor site; more female patients if breast tumor is the most common primary, while male predominance if prostate cancer primary found to be more. A few studies documented male majority in bone metastasis, whereas female preponderance also noticed in some analyses[13,27,31-33]. Three-fourths of our patients were from rural background. This data strongly matched with the data from Korean study, both India and Korea are Asian country with majority of people living in rural region[32]. Our analysis showed that lung cancer was the most common primary site (37%) followed by breast and prostate in decreasing frequency. These data were different from that were mentioned in the literature, where either breast or prostate was the most common primary[24,25,31-33]. However, other studies from the same country also denoted lung cancer as the most common primary metastasizing to bone[7,26]. Around 40% of

Table 2. Baseline tumor profiles (both primary and metastatic) of bone metastasis patients in all three groups

Characteristics	Group I (%)	Group II (%)	Group III (%)
Primary tumor	B: 06 (30)	B: 07 (35)	B: 05 (25)
	L: 08 (40)	L: 05 (25)	L: 09 (45)
	P: 04 (20)	P: 05 (25)	P: 04 (20)
	O: 02 (10)	O: 03 (15)	O: 02 (10)
Involved metastatic bone	Pe: 05 (25)	Pe: 06 (30)	Pe: 04 (20)
	St: 01 (05)	S: 02 (10)	S: 02 (10)
	V: 10 (50)	V: 07 (35)	V: 08 (40)
	O: 04 (20)	O: 05 (25)	O: 06 (30)
Number of bone metastasis	S: 12 (60)	S: 11 (55)	S: 14 (70)
	M: 08 (40)	M: 09 (45)	M: 06 (30)
Appearance of bone metastasis	Sy: 09 (45)	Sy: 06 (30)	Sy: 08 (40)
	N-Sy: 11 (55)	N-Sy: 14 (70)	N-Sy: 12 (60)
Involvement of other distant sites (lung/liver/brain etc.)	Y: 13 (65)	Y: 15 (75)	Y: 11 (55)
	N: 07 (35)	N: 05 (25)	N: 09 (45)

B: Breast; L: Lung; O: Other; M: Multiple; N: No; P: Prostate; Pe: Pelvis; S: Single; St: Sternum; Sy: Synchronous; N-Sy: Non-synchronous; V: Vertebrae; Y: Yes.

Table 3. Post-treatment observation of bone metastasis patients in all three groups

Characteristics	Group I (%)	Group II (%)	Group III (%)
Overall pain response	13 (65)	16 (80)	17 (85)
Complete pain relief	03 (15)	04 (20)	04 (20)
Mean duration of overall pain response	24.5 weeks	21.3 weeks	22.6 weeks
Improved performance status	02 (10)	03 (15)	04 (20)
Decreased analgesics requirements	11 (55)	14 (70)	13 (65)
Reirradiation	03 (15)	04 (20)	01 (05)

patients in our study had bone metastasis initially, that is, at the time of primary cancer diagnosis. This also matched nearly with the similar data from another Asian country[32]. Nearly two-third of patients (65%) of our study cohort had bone metastasis in vertebrae and pelvis, bones rich in red bone marrow. This finding is in consistent with existing literature[21]. Overall reirradiation rate (13.33%) in our analysis matched closely with the reirradiation rate of single fraction RT (14%) in a 5-year retrospective study conducted in Belgium[34].

A few limitations are there in our study. Among these, the significant drawback was very small sample size, that is, only 60 patients. Another limiting factor could be not evaluating the association of other treatment modalities such as systemic therapies and bisphosphonates along with radiation in assessing the primary objectives. On contrary, the interesting fact of our study was that all three groups have nearly equal schedules in terms of fractions and radiobiological perspective. Inclusion of all metastatic bony site irrespective of subsite specification is also unicity of our analysis.

Conclusion

It was observed that all three schedules provided good palliation in the painful bone metastases. However, Schedules II and III were found to be more effective in comparison to Schedule I with better overall pain relief, complete pain relief, and improved performance status. In conclusion, it can be stated that all three

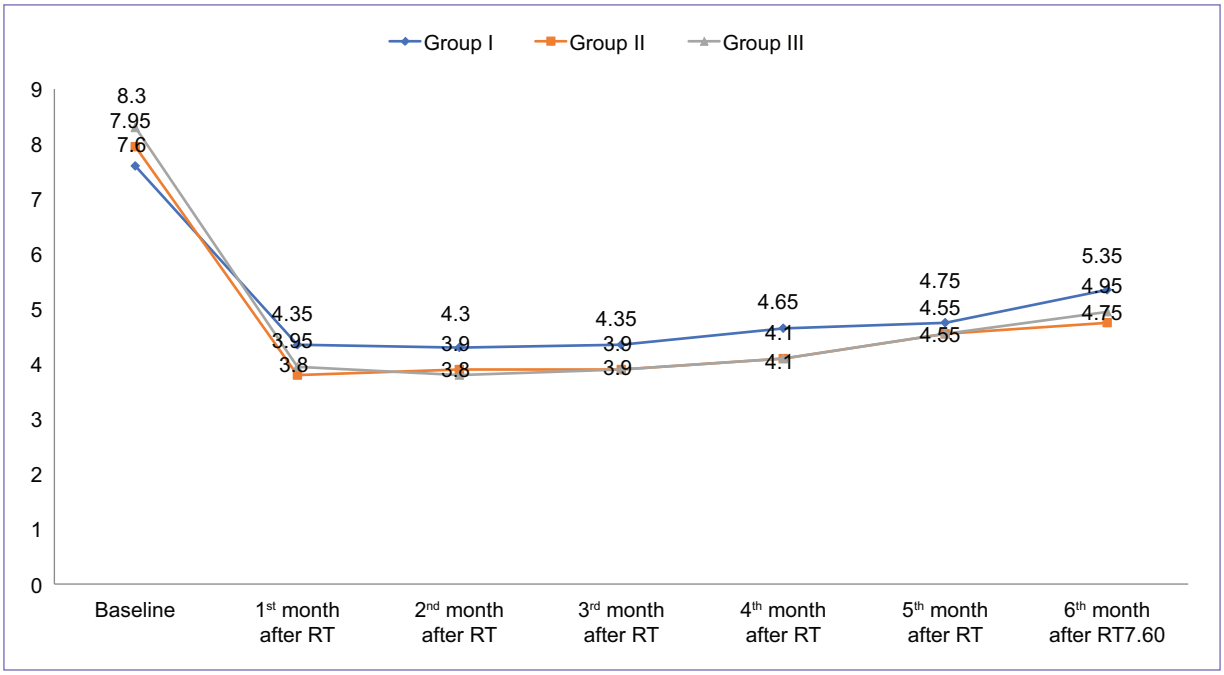

Figure 2. Mean pain score in patients of bone metastasis in all the three groups before and after radiation therapy.

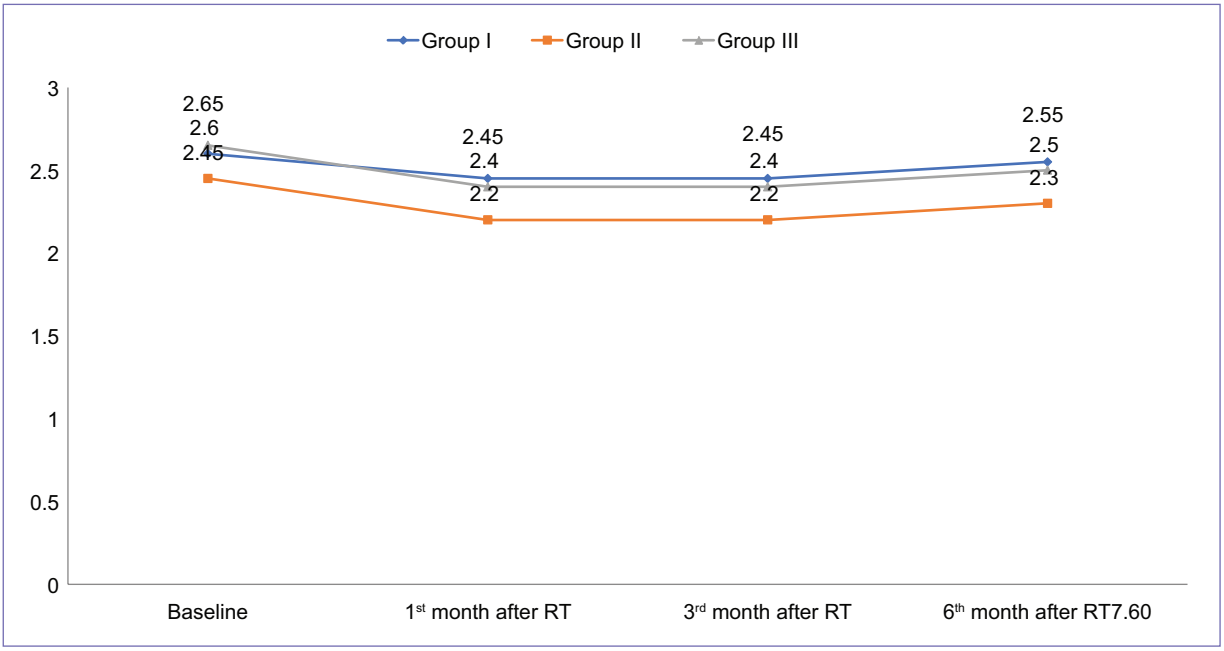

Figure 3. Mean ECOG (Eastern Cooperative Oncology Group) performance status of bone metastasis patients in all the three groups before and after radiation therapy.

schedules of palliative EBRT can be given in painful bone metastasis patients depending on patient tolerability and compliance. This single or two fractions' schedules in palliation of bone metastasis in limited resource settings are very useful, both for patients and health-care providers

Table 4. Various studies conducted in different parts of the world to compare SS and MF radiation dose schedules in painful bone metastases

Study (year)	SS dose schedules	MF dose schedules	Number of patients/lesions	Response
Amichetti et al.[13] (2004)	8 Gy	20 Gy/5 fractions	SS: 87 MF: 59	– Overall pain response SS: 67% MF: 60% – PS improvement SS: 44% MF: 47% – Median OS SS: 9 months MF: 10 months
Hamouda et al.[14] (2007)	8 Gy	40 Gy/20 fractions	SS: 50 MF: 52	– Pain relief SS: 84% MF: 88.5% – Complete pain relief SS: 46% MF: 48.1% – Pain relief duration SS: 12 weeks MF: 13.5 weeks
Amouzegar-Hashemi et al.[15] (2008)	8 Gy	30 Gy/10 fractions	SS: 27 MF: 31	– Overall pain response SS: 78% MF: 65% – Mean pain reduction SS: 1.1 MF: 1.1
Anter[16] (2015)	8 Gy	20 Gy/5 fractions	SS: 51 MF: 49	– Complete pain relief SS: 18% MF: 22% – Partial pain relief SS: 56.8% MF: 52.2%
Arnalot et al.[17] (2008)	8 Gy	30 Gy/10 fractions	SS: 78 MF: 82	– Overall pain response SS: 75% MF: 86% – Net pain relief SS: 68% MF: 71% – Mean OS SS: 28 weeks MF: 33 weeks
Majumder et al.[25] (2012)	8 Gy	30 Gy/10 fractions	SS: 31 MF: 33	– Partial pain response SS: 76.9% MF: 84.6% – Progressive pain SS: 23.1% MF: 15.4%
Jilla et al.[26] (2014)	8 Gy	20 Gy/5 fractions (MF 1) 30 Gy/10 fractions (MF 2)	SS: 15 MF 1: 15 MF 2: 15	– Overall pain response SS: 78.6% MF 1: 80% MF 2: 80% – PS improvement SS: 78.6% MF 1: 80% MF 2: 80%
Kapoor et al.[27] (2015)	8 Gy	30 Gy/10 fractions	SS: 116 MF: 71	– Overall pain response SS: 58% MF: 60% – Progressive pain SS: 7% MF: 9%

OS: Overall survival; MF: Multi-fractions; PS: Performance status; SS: Single session.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the code of ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. This is a prospective analytical study and written informed consent was taken from all the participating patients after explaining them the relevance of the study in their native language.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

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ORIGINAL ARTICLE

Breast cancer survival in Guerrero: oncologic care and geographic disparities in Mexico

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Abstract

Background: *Breast cancer (BC) represents a public health concern among women. Despite the incidence and disparities in economic status, the state of Guerrero in Mexico demonstrates a lower BC mortality rate.* **Objective:** *This study investigates the epidemiological characteristics, treatment modalities, and survival outcomes of BC patients in Guerrero, and compares these findings with national data.* **Method:** *A retrospective cohort of 923 BC patients treated at the Instituto Estatal de Cancerología Dr. Arturo Beltrán Ortega, from 2010 to 2018 was analyzed. To determine the prognostic factors affecting survival, we employed overall survival analysis and the Cox proportional hazards model.* **Results:** *The 5-year survival rate was of 73% (CI 95%: 69-76). BC patients ≤ 40 years exhibited lower survival rates and a 1.5-fold higher risk of mortality. When comparing the triple-negative subtype to HER2-positive tumors, no significant differences in reducing the risk of death were observed.* **Conclusion:** *Despite a higher prevalence of aggressive molecular subtypes in Guerrero, patients share clinical and epidemiological features with their counterparts in other Mexican regions.*

Keywords: *Breast cancer. Mexico. Regions. Molecular subtype. Survival time.*

Supervivencia del cáncer de mama en Guerrero: atención oncológica y disparidades geográficas en México

Resumen

Antecedentes: *El cáncer de mama (CM) representa un problema de salud pública entre las mujeres. A pesar de la incidencia y las disparidades en el estatus económico, el estado de Guerrero en México demuestra una tasa de mortalidad por cáncer de mama más baja.* **Objetivo:** *Este estudio investiga las características epidemiológicas, las modalidades de tratamiento y los resultados de supervivencia de los pacientes con CM en Guerrero y compara estos hallazgos con datos nacionales.* **Método:** *Se analizó una cohorte retrospectiva de 923 pacientes con CM atendidos en el Instituto Estatal de Cancerología Dr. Arturo Beltrán Ortega, del 2010 al 2018. Para determinar los factores pronósticos que afectan la supervivencia, empleamos el análisis de supervivencia general y el modelo de riesgos proporcionales de Cox.* **Resultados:** *La tasa de supervivencia a 5 años fue del 73% (IC 95%: 69-76). Los pacientes con BC ≤ 40 años mostraron tasas de supervivencia más bajas y un riesgo de mortalidad 1.5 veces mayor. Al comparar el subtipo triple negativo con los tumores HER2 positivos, no se observaron diferencias significativas en la reducción del riesgo de muerte.* **Conclusión:** *A pesar de una mayor prevalencia de subtipos moleculares agresivos en Guerrero, los pacientes comparten características clínicas y epidemiológicas con sus homólogos de otras regiones mexicanas.*

Palabras clave: *Cáncer de mama. México. Regiones. Subtipo molecular. Tiempo de supervivencia.*

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Introduction

Breast cancer (BC) is the most common malignant tumor among women globally and remains the leading cause of cancer-related death. Despite advancements in diagnosis and treatment, developing countries bear a significant burden, accounting for 45% of global incidence and 55% of deaths. In Mexico, the estimated incidence and mortality rates for BC are 39.5 and 9.9 cases/100,000, respectively[1,2]. BC is the most prevalent neoplasm in Mexican women[3], and institutions such as Instituto Nacional de Cancerología (INCan) and Fundación de Cáncer de Mama (FUCAM) have contributed to understanding the clinical and epidemiological characteristics of the populations they serve[4-7]. These studies highlight the significance of clinicopathological factors in disease prognosis[5,7,8]. Despite this, the impact of the health system and the economic-related factors, so important for disadvantaged people, in the diagnosis, treatment, and mortality of BC, has been neglected. These factors are relevant, as Mexico has one of the highest levels of inequality in the OECD with a Gini index of 45[9,10]. Therefore, there is still a need for regional-level epidemiological studies to comprehend the impact of biological, social, and cultural disparities on BC incidence and mortality.

Therefore, sharing our experience in treating this disease within the population of Guerrero state holds great value. Notably, the Colima Consensus reported a low BC mortality rate in spite of a high poverty proportion (38.7% moderate poverty and 26.9% extreme poverty)[3,11]. Guerrero state is characterized by a predominantly native American (70.9%) and Afro-descendant (3.2%) genetic makeup, particularly in the coastal regions of Acapulco and Costa Chica, which have significant public health implications[4,12,13]. This study aims to describe the clinical, pathological, and epidemiological characteristics of BC patients in Guerrero and compare them with existing reports on the Mexican population.

Material and methods

We conducted a retrospective review of clinical records from the Instituto Estatal de Cancerología (IECan) Dr. Arturo Beltran Ortega in Acapulco, Guerrero, Mexico, covering the period from January 2010 to December 2018. The study focused on patients diagnosed with BC. Demographic data, clinicopathological characteristics, treatment modalities, histopathological type, immunohistochemistry (IHC) profile, and current patient status were extracted and analyzed. Histopathologic evaluations were performed by pathologists, and the presence of hormone receptors (HRs) was determined using the H-Score[3] method through IHC analysis. Descriptive statistics were computed for each variable. Overall survival (OS) and disease-free survival (DFS) were estimated using the Kaplan-Meier method, and the log-rank test was employed to assess statistical differences between survival functions based on clinical characteristics. Furthermore, we utilized an adjusted Cox proportional hazards model (HRM) to identify clinical variables that could predict survival in the study population. Statistical significance was set at $p < 0.05$. All data analyses were conducted using SPSS v22 software (SPSS, Inc., Chicago, IL, USA).

Results

A total of 923 clinical records were analyzed, encompassing a population consisting of 91.3% women from the seven regions of the state of Guerrero. The remaining 8.7% comprised patients from neighboring southeast states. Table 1 presents the demographic and reproductive risk factors. The mean age at the time of BC diagnosis was 53.0 (±12.0) years. The population displayed mean menarche at 12.9 ± 1.3 years, mean age of first pregnancy at 21.6 ± 5.2 years, mean age at menopause at 45.7 ± 5.1 years, and 236 (25.6%) patients reported contraceptive use. Common comorbidities among the population included diabetes and hypertension. A history of first-degree family cancer was observed in 17.2% of the population. The clinical stage at diagnosis predominantly represented stage II (37.9%) and stage III (36.1%). Regarding histologic grade, well-differentiated or grade I tumors accounted for 7.2% of the total, moderately differentiated (grade II) for 45.9%, and poorly differentiated (grade III) for 43.6%. HR-positive tumors comprised 79% of cases, with the Luminal A subtype being the most common (35.1%, n = 324), followed by Luminal B (15.9%, n = 147), Luminal B human epidermal growth factor receptor 2 (HER2) positive (14.4%, n = 133), HER2 positive (13.5%, n = 125), and triple negative (21%, n = 194). Mastectomy was performed in 96.9% of the population, and 89.2% received chemotherapy, with 49.8% receiving adjuvant and 39.4% neoadjuvant chemotherapy. Furthermore, 60.3% of the population underwent radiotherapy (Table 1).

The median OS of the cohort was 49 months, with a 5-year OS rate of 73% (95% confidence interval [CI], 69-76). Among patients with metastatic disease, the 5-year OS rate was 67% (95% CI, 63-70). Analysis of

Table 1. Description of demographic and clinical pathological characteristics of breast cancer patients

Variable	Frequency (%)
Age, years (mean ± standard deviation)	53.0 ± 12.0
Median (rank), years	52 (19-93)
Family history of cancer	
No	764 (82.8)
Yes	159 (17.2)
Comorbidity	
Diabetes	64 (6.9)
Hypertension (only)	137 (14.8)
Diabetes and hypertension	65 (7.0)
Other	13 (1.4)
Reproductive factors	
Age at menarche, years	12.9 ± 1.3
Age first pregnancy, years	21.6 ± 5.2
Oral contraceptive use (yes)	236 (25.6)
Age at menopause, years	45.7 ± 5.1
Lymph node metastasis	
Positive	467 (51)
Negative	432 (47)
Stage	
I	32 (3.5)
II	350 (37.9)
III	333 (36.1)
IV	132 (14.3)
Molecular subtype	
Luminal A (HR+/HER2–)	324 (35.1)
Luminal B (HR ± /HER2–)	147 (15.9)
Luminal B HER2 positive (HR ± /HER2+)	133 (14.4)
HER2 positive (HR–/HER2+)	125 (13.5)
Triple negative (HR–/HER2–)	194 (21)
Surgical treatment	
Mastectomy	894 (96.9)
Breast-conserving surgery	29 (3.1)
Chemotherapy	
Adjuvant	413 (45)
Neoadjuvant	295 (32)
Palliative	129 (14)
No chemotherapy	86 (9)
Radiotherapy	
Yes	557 (60.3)
No	366 (39.6)

Mean ± standard deviation. HR: hormone receptors; HER2: human epidermal growth factor receptor 2.

5-year survival revealed significant differences based on age at diagnosis ($p < 0.0001$). Patients older than 40 years exhibited higher median survival, with a 76% survival rate. In comparison, the survival rates were 63% for patients aged 31-40 years and 12% for those ≤ 30 years old. Furthermore, stage IV patients had a lower survival rate of 29% (Table 2).

Examining survival in relation to tumor differentiation grade, we observed a 80% survival rate for grades I and II, whereas grade III tumors showed a 64% survival rate. Molecular subtype analysis demonstrated a 5-year survival of 84% for Luminal A tumors, 81% for Luminal B tumors, 70% for Luminal B HER2-positive tumors, 59% for HER2-positive tumors, and 58% for triple-negative tumors. Among patients with metastases, the observed survival rate was 35% (Table 2).

Adjusted multivariate analysis, accounting for age at diagnosis, histologic grade, clinical stage, molecular subtype, and metastasis, revealed a 1.5-fold increased risk of BC-related death for patients diagnosed before 40 years of age. Luminal A and Luminal B tumors were associated with a 61% and 50% decrease in the risk of death, respectively, while Luminal B HER2-positive tumors showed a 40% decrease. However, no significant difference was observed in reducing the risk of death between Triple-negative and HER2-positive subtypes. Notably, the presence of metastasis increased the risk of death by 27 fold (Table 3).

Subsequently, we compared our findings from the IECan Dr. Arturo Beltrán Ortega (IECan) with data from other institutions, including the INCan[7,8], the FUCAM[6,14], the breast clinic of the Instituto Jalisciense de Cancerología, Guadalajara (IJC)[1], and the Centro Estatal de Cancerología, Veracruz (CECan)[15]. Our patients exhibited demographic and clinical characteristics that were similar to those reported in other regional studies. The age at diagnosis, family history, and histologic type, specifically ductal carcinoma, were comparable across populations. The distribution of molecular subtypes, however, showed slight variations (Table 4).

In our study (IECan), the luminal subtype (Luminal A and Luminal B HER2 positive) accounted for 65.4% of the tumors, similar to the prevalence observed in CECan, IJC, and INCan, but not reported by FUCAM (76.6%). Concerning the HER2+ tumor subtype, our study found a prevalence of 14%, slightly higher than the 8.7% reported by FUCAM and the 10.5% observed in IJC and CECan. Notably, HER2-positive tumors were more prevalent in INCan (23%) compared to our study (13%) (Table 4). Finally, the triple-negative subtype in our study exhibited a prevalence of 21%, which aligned with the prevalence reported by IJC and was slightly lower than the 23.5% observed in CECan. Interestingly, the prevalence of the triple-negative subtype in INCan (16%) and FUCAM (15%) was lower compared to the data from other national and international studies[8,12,14,16].

In terms of mean follow-up duration, IECan demonstrated a significantly longer period of follow-up compared

Table 2. Overall survival from breast cancer diagnosis to date of last contact or death

Variable	Total	Events	Percent 1-year OS	Percent 3-year OS	Percent 5-year OS	p
Global analysis	923	244	97 (96-98)	84 (82-87)	73 (69-76)	
Age						
19-30	21	15	95 (85-100)	45 (27-75)	12 (2.4-63)	0.0001
31-40	120	44	94 (90-98)	70 (62-79)	63 (54-73)	
41-50	264	67	98 (96-100)	85 (80-89)	75 (69-81)	
51-60	275	70	97 (96-99)	88 (84-92)	76 (71-83)	
61-70	167	33	99 (97-100)	91 (84-92)	75 (67-84)	
> 70	76	15	96 (92-100)	87 (80-95)	80 (70-91)	
40-year-old threshold						
≤ 40	141	59	94 (90-98)	66 (58-75)	56(48-66)	0.0001
> 40	782	185	98 (97-99)	87 (85-90)	76 (7280)	
Histologic grade						
Low	66	12	94 (88-100)	89 (81-97)	80 (68-93)	0.0001
Intermediate	424	78	98 (97-100)	90 (87-93)	80 (75-85)	
High	402	145	96 (95-98)	77 (73-81)	64 (59-70)	
Molecular subtype						
Luminal A (HR+/HER2–)	324	59	99 (98-100)	94 (92-97)	84 (79-89)	0.0001
Luminal B (HR ± /HER2)	147	23	99 (97-100)	91 (87-96)	81 (73-90)	
Luminal B HER2 positive (HR ± /HER2+)	133	42	99 (98-100)	82 (76-89)	70 (62-80)	
HER2 positive (HR–/HER2+)	125	48	93 (88-97)	73 (65-81)	59 (50-70)	
Triple negative (HR–/HER2–)	194	72	95 (92-98)	70 (63-77)	58 (51-67)	
Metastasis						
Yes	290	228	94 (91-97)	57 (51-63)	35 (29-40)	0.0001
No	633	16	99 (98-100)	98 (97-99)	97 (95-98)	

Percentage % and (95% CI). HR: Hormonal receptor; HER2: human epidermal growth factor receptor 2; OS: overall survival.

to other hospitals. However, the OS and DFS rates at 5 years were lower in IECan than in other institutions, except for IJC. When comparing our survival results, we observed a median follow-up duration of 49 months, which was higher than the reported durations of 40.5 months in INCan, 46.8 months in IJC, and 28 months in FUCAM. The 5-year OS in our study was 73%, similar to the rate reported by IJC (78.5%), but slightly lower than the rates reported by INCan and FUCAM.

Regarding survival by subtypes, IECan showed 84% and 81% survival for the luminal subtypes (Luminal A and Luminal B), which were slightly lower than the 89% reported by FUCAM (Table 4). In addition, IECan reported a survival rate of 70% for the Luminal B HER2-positive subtype, while FUCAM reported 81.9%. In the HER2-positive subtype, our patients exhibited a 59% survival rate, which differed from the 74.9% reported by FUCAM. The survival rate for the triple-negative subtype in IECan was 58%, contrasting with the 69.5% reported by FUCAM, while IJC reported a 52.9% survival rate[1,8,14].

In summary, IECan displayed inferior survival rates across all subtypes compared to FUCAM. The differences in tumor subtype observed in our population, as compared to populations from other states, provide essential data for studying tumor heterogeneity.

Discussion

BC detection in Mexican patients often occurs at advanced stages of the disease (III and IV). In terms of pathology features, prevalent characteristics include ductal histology, intermediate or high-grade tumors, and HR-positive tumors[7,8,17]. These results differ from reports issued by other Mexican states, such as Jalisco (IJC), Mexico City, and Veracruz (CECan), which have significantly contributed to the understanding of BC epidemiology in our country.

The variation observed in previous reports reflects the heterogeneity of the disease and its outcomes across different geographical regions. Histological grade is recognized as a determining factor for the biological behavior of tumors and serves as a useful prognostic tool. Moreover, estrogen and progesterone

Table 3. Multivariate analysis for breast cancer-specific survival (Cox proportional regression model)

Variable	HR	(95% CI)	p	HR	(95% CI)	p
Age, years						
≤ 40	2.2	1.62-2.89	0.0001	1.54	1.14-2.09	0.005
> 40	1	1	1	1	1	1
Clinical stage						
I	1	1	1	1	1	1
II	1.03	0.31-3.37	0.95	1.05	0.27-4.01	0.94
III	3.1	0.98-9.86	0.052	1.19	0.32-4.41	0.75
IV	13.2	4.20-41.79	0.0001	1.84	0.50-6.83	0.36
Histologic grade						
Low	1	1	1	1	1	1
Intermediate	0.89	0.49-1.60	0.69	0.69	0.38-1.26	0.23
High	1.63	0.92-2.88	0.08	0.80	0.45-1.43	0.45
Breast cancer subtype						
Luminal A (HR+/HER2–)	0.37	0.26-0.53	0.0001	0.39	0.27-0.56	0.0001
Luminal B (HR ± /HER2)	0.38	0.24-0.60	0.0001	0.50	0.31-0.79	0.004
Luminal B HER2 positive (HR ± /HER2+)	0.64	0.43-0.94	0.02	0.60	0.40-0.90	0.015
HER2 positive (HR–/HER2+)	1	1	1	1	1	1
Triple negative (HR–/HER2)	0.94	0.65-1.36	0.77	1.07	0.73-1.56	0.71
Metastasis						
No	1	1	1	1	1	1
Yes	36.2	21.80-60	< 0.0001	27.45	16-46.9	0.0001

HR: Hormonal receptor; HER2: human epidermal growth factor receptor 2; CI: confidence interval.

receptors, along with overexpression of the HER-2 oncoprotein, are considered prognostic and predictive factors[18]. Our analysis of subtypes was based on the immunohistochemical approach, allowing us to gain a comprehensive understanding of their behavior and establish differences between them. Our data align closely with the descriptions provided by CECan and show slight variations compared to IJC, INCan, and FUCAM reports. Notably, the proportion of triple-negative tumors in our population is higher than that reported by national institutions (INCan and FUCAM). However, this proportion is like the data reported by CECan. This finding is noteworthy because the proportion of Afro-descendants in Veracruz (CECan) is higher compared to other regions, and the economic conditions are similar to Guerrero[15,19].

At present, there is a lack of studies in our country that investigates the ancestral background of BC patients in specific populations. Understanding the tumor heterogeneity and prognosis in BC patients can be aided by considering the ancestral diversity within these populations. In Guerrero, the population exhibits mixed ethnic diversity, with a significant presence of self-identified native Americans and Afro-descendants, particularly in the coastal regions of Acapulco and Costa Chica[12]. The African ancestry in Mexico has been reported as 1.8 ± 3.5% (mean ± standard deviation), while in Mexico City, an African component of 3.5% has been described according to HapMap[20]. In states such as Veracruz, the African ancestry is approximately 2 ± 4.2%, while in Guerrero, it reaches 4.1 ± 6.1%[19].

Furthermore, the majority of our BC patients come from Costa Chica and Costa Grande, which have the highest proportion of Afro-descendant population (> 7%)[12]. This information holds significance in public health, as studies suggest that African American women (AA) have a higher predisposition to early-onset aggressive BC[18,21]. Churpek et al. in 2015 reported that 80% of AA BC patients carried mutations in the *BRCA1* and *BRCA2* genes, while 20% had mutations in *PALB2*, *CHEK2*, *BARD1*, *ATM*, *PTEN*, or *TP53* genes[18]. These regional differences in mortality may be associated with causative or risk-influencing genetic factors or protective effects conferred by the genetic background.

On the other hand, in Mexico, most cases are diagnosed in advanced stages (50-60%), far above than reported for countries with early detection programs[6,14]. In 2011, Bright et al. studied the influence of health system factors as responsible for the delay in BC diagnosis in Mexico. The authors found that the median time from symptom onset to treatment was 5.2 months:7.5 months for early clinical stages and 4 months for advanced clinical

Table 4. Patient demographics and clinical outcomes in different cancer institutions in Mexico

Variable	IECan (This study)	INCan (7)	INCan (8)	FUCAM (6,12)	IJC (1)		CECan (13)
	n = 923	n = 4300	n = 4316	n = 3762	n = 172		n = 1446
Global							
Age, years (mean ± standard deviation)	53 ± 12	52 ± 12.1	ND	53.7 ± 12.2	51.4		52.5 ± 12.1
Age							
≤ 40	15.3	15.3	15.4	13.3	ND		15.2
> 40	84.7	84.7	84.6	86.7	ND		84.8
Family history of cancer							
Yes	17.2	ND	ND	9.5	45.9		ND
No	82.8	ND	ND	90.5	54.1		ND
Histopathology							
Ductal	82.7	85.1	ND	79.7	87.2		ND
Lobular	4.1	9.4	ND	7.8	9.9		ND
Other	13.2	5.5	ND	12.5	2.9		ND
Histologic grade							
Low	7.2	18.5	15.7	9.1	10.7		16.4
Intermediate	45.9	30.1	29.1	54.1	56.5		83.6
High	43.6	51.3	55.25	34.6	32.7		
Lymph node metastasis							
Positive	51	ND	ND	ND	69		43.2
Negative	47	ND	ND	ND	5.9		56.8
Clinical stage							
I	3.5	14.2	12	36.4	8.7		41.6
II	37.9	36.6	35.15		33.1		
III	36.1	36.2	39.2	45.2	52.3		58.4
IV	14.3	12.9	13.65	7.7	5.8		
Molecular subtype							
Luminal A (HR+/HER2–)	35.1	60.7	56.95	65.7	55.8		43.9
Luminal B (HR ± /HER2)	15.9				12.2		21.1
Luminal B HER2 positive (HR ± /HER2+)	14.4			10.9			
HER2 positive (HR–/HER2+)	13.5	23.2	24.1	8.7	10.5		11.2
Triple negative (HR–/HER2–)	21	16	18.9	14.6	21.5		23.8
Metastasis							
Yes	33	24	ND	ND	24.4		13.5
No	67	76	ND	ND	75.6		86.5
Clinical outcomes							
Median follow-up	49		40.5	40	28	ND	ND
5-year OS	73		82	81	83.1	78.5	ND
5-year DFS	67		ND	80.6	81.8	46.8	ND

INCan: Instituto Nacional de Cancerología; FUCAM: Fundación de Cáncer de Mama; IJC: Instituto Jalisciense de Cancerología; IECan: Instituto Estatal de Cancerología Dr. Arturo Beltran Ortega, CECan. Centro Estatal de Cancerología de Veracruz. ND: no data; HR: hormonal receptor; HER2: human epidermal growth factor receptor 2; OS: overall survival, DFS: disease-free survival.

stages. In contrast, among high-income countries, the median total intervals range between 30 and 48 days, and > 60% of patients begin treatment in the first 3 months after symptom discovery[22,23]. The findings suggest that in developing countries as Mexico, the prolonged referral time from primary to specialty care accounts for most of the delay, especially for patients in early stages[22,24].

With respect to our study, the diagnosis occurs in advanced stages of the disease, and the time that elapses between the symptoms and the first consultation is approximately 9-12 months. In most cases, the patients were aware of the symptoms, but not of the importance of the diagnosis, so they did not prioritize seeking medical help. These findings could be attributed to low educational level related to preventive care, but also related

to disease's perception, the influence of cultural/religious practices, but also to the preference of alternative medicine in a daily basis. Therefore, the delay in diagnosis could be not always associated with the health institution's deficiencies but more related to the social factors.

Considering this, in Mexico and in our study, the features associated with BC lethality can be attributable to the high rate of population marginalization and result of a limitations in educational and health-care access. Despite this, other possible causes of these differences can be related to factors such as population aging, the "westernization" of the lifestyle, and the genetic background of each population[3]. Interestingly, the *per capita* income in Guerrero is one of the lowest of Mexico[16].

Finally, one of the main challenges encountered in this study relates to the specific population under analysis. The IECan primarily caters to marginalized populations within Guerrero. The patients treated do not receive medical attention from national health institutions such as IMSS or ISSSTE, which provide medical services to private or public Mexican workers. National statistics indicate that in Mexican municipalities with over 10% of the Afro-descendant population, approximately 76% of the population lacks IMSS or ISSSTE coverage, while for the general population, this figure is around 41%[25]. Therefore, it is possible that the percentage of Afro-descendants in our study population is higher than reported in typical BC studies. Further genetic and epidemiological analyses are necessary to elucidate the factors contributing to the mortality rates observed in this region.

Conclusion

The characterization of the clinical and epidemiological profiles of different regions is crucial for identifying risk and prognostic factors, which in turn inform strategies for individualized treatment decision-making. Regional data, particularly in areas with diverse ethnic origins and socioeconomic marginalization, are essential for developing targeted approaches to prevention and early diagnosis, thereby improving the care of BC patients. While Guerrero exhibits marginalization, most epidemiological parameters align with those reported in national studies. However, the frequency of the triple-negative subtype is unique to the population in this study. Therefore, the local disparities in BC mortality rates in Guerrero remain unexplained and necessitate further analysis. Nevertheless, the local and regional information from Guerrero will be invaluable for public health decision-makers.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of people and animals. The authors declare that no experiments have been carried out on humans or animals for this research.

Data confidentiality. The authors declare that they have followed their workplace's protocols regarding the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for the analysis and publication of routinely obtained clinical data. Informed consent from the patients was not required as it was a retrospective observational study.

Use of artificial intelligence to generate texts. The authors declare that they have not used any type of generative artificial intelligence in the writing of this manuscript or for the creation of figures, graphs, tables, or their corresponding captions or legends.

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ORIGINAL ARTICLE

Cost reduction for cancer drug treatment with a vial sharing strategy in a centralized preparation unit

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Abstract

Background: *Rising cancer rates and expensive drugs have inflated treatment costs. Medication wastage constitutes 5% of drug expenditure. Effective cost containment strategies are essential.* **Objective:** *To implement and assess a cost-cutting strategy for oncology drugs.* **Methods:** *Doses and quantities of oncology drugs were analyzed from January to June of 2022, calculating the total usage and costs by comparing with a decentralized system to estimate the economic impact.* **Results:** *Sharing vials achieved a savings of $9,000,705.64MNX. Centralized preparation totaled $52,775,243.24MNX, with a 14% reduction in expenses.* **Discussion:** *This pioneering study in Mexico aligns with similar reductions in other countries, underscoring the importance of applying cost containment strategies in developing nations.* **Conclusion:** *Implementing a centralized preparation unit and vial sharing offer economic benefits, with further research needed to optimize their effectiveness.*

Keywords: *Pharmacoeconomics. Cost savings. Centralized preparation unit. Vial sharing. Oncology medications.*

Reducción de costos en el tratamiento de fármacos contra el cáncer mediante una estrategia de compartición de viales en una unidad de preparación centralizada

Resumen

Antecedentes: *El aumento de casos de cáncer y los costosos tratamientos incrementan los gastos sanitarios. Se desperdician medicamentos equivalentes al 5% del gasto anual. Es importante implementar estrategias de contención de costos.* **Objetivo:** *Implementar y evaluar una estrategia de reducción de costos en medicamentos oncológicos.* **Métodos:** *Se analizaron dosis y cantidades de medicamentos oncológicos de enero a junio de 2022, calculando el uso total y costos comparando con un sistema descentralizado para estimar el impacto económico.* **Resultados:** *Compartir viales logró un ahorro de $9,000,705.64MNX. La preparación centralizada totalizó $52,775,243.24MNX, con una reducción del 14% en gastos.* **Discusión:** *Este estudio pionero en México coincide con reducciones similares en otros países, resaltando la importancia de aplicar estrategias de contención de costos en países en desarrollo.* **Conclusión:** *La implementación de una unidad de preparación centralizada y la compartición de viales ofrecen beneficios económicos. Se requiere investigación adicional para optimizar su eficacia.*

Palabras clave: *Farmacoeconomía. Ahorro de costos. Unidad de preparación centralizada. Compartición de viales. Medicamentos oncológicos.*

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Introduction

Pharmacoeconomics is a discipline that combines economics and medicine to analyze the relationship between the costs and benefits of pharmacological treatments[1,2]. Its objective is to improve decision-making related to resource allocation in the health-care system[3,4]. However, one of the major challenges currently faced by pharmacoeconomics is the high cost of cancer medications.

This problem has been intensified due to the increasing prevalence of cancer, which, in 2020, was estimated to cause nearly 10 million deaths, with breast cancer being the leading cause[5]. The cost of oncology medications remains a critical issue for health-care systems worldwide and global annual spending on medications has been on the rise in recent years. In addition, it is estimated that medication wastage accounts for 5% of total expenditure[6], largely due to suboptimal medication utilization.

The proportion of drug-related expenses is higher in oncology compared to other medical specialties. The introduction of new medications, such as bevacizumab, cetuximab, and trastuzumab, has contributed to a 20% increase in cancer drug costs in the United States between 2005 and 2006[2,3]. Similar trends have been observed in other countries[3].

The annual economic cost of cancer is estimated to reach 1.16 trillion dollars worldwide. Therefore, an investment of 11 billion dollars in prevention strategies has been proposed in different countries, which could potentially save up to 100 billion dollars in cancer treatments[7].

In Mexico, in 2021, the United Nations Office for Project Services acquired 132 key oncology medications, equivalent to 6,929,197 units, with an investment of 11,795 million Mexican pesos or around 688 million dollars[8]. In addition, the Ministry of Foreign Affairs obtained 27 oncology medication keys, including 23 high-consumption, and four complementary supplies, through the Mexican embassies in India, Argentina, Korea, Canada, France, Germany, and Cuba[8].

Given this landscape, it is crucial to develop strategies to reduce the cost of oncology medications. One technique that has proven to be effective is vial sharing, which involves administering individualized doses of the same drug to different patients using a single vial instead of a separate vial for each patient[9]. This practice takes place in a centralized preparation unit, where individual doses are prepared under quality conditions[9,10].

Several studies have demonstrated that the vial sharing strategy can significantly reduce cancer treatment costs, estimating potential savings of 30-45% in oncology medication costs[8-12].

Objectives

The objective of the article is to implement and evaluate a cost reduction strategy for oncology drugs. The study aims to identify opportunities to optimize resources and decrease expenses associated with cancer treatment by implementing a vial sharing strategy in a centralized preparation unit. The effects of this strategy in terms of cost reduction and its impact on the quality of care for cancer patients will be investigated. The article seeks to provide scientific and practical evidence regarding the feasibility and benefits of this strategy in the efficient management of resources in the context of oncology pharmacological treatment.

Materials and methods

This was an observational study aimed at determining the economic impact of implementing a centralized preparation unit and vial sharing strategy at a tertiary-level hospital in Mexico City. To achieve this objective, the doses and quantity specifications of medications used in patients receiving cancer treatment were investigated from January to June 2022, with a total of 38 drugs analyzed. The variables used included patient age and sex, body surface area, cancer type, chemotherapy regimen employed, medication, and prescribed dose per day of treatment.

Based on these findings, the total quantity of each medication used was calculated, and the minimum preparation cost for each specified combination corresponding to the total cost was determined. Subsequently, the cost of these treatments was estimated if an individual vial preparation strategy and decentralized system had been used.

This study enabled us to determine the potential economic savings associated with implementing the vial sharing strategy and centralized preparation unit in cancer treatment at this specific hospital. By examining the differences in costs, we were able to assess the economic impact of these strategies.

Study data were obtained from the evaluation of prescriptions by the health-care provider and recorded in an Excel® spreadsheet. The results for quantitative variables were described as mean, median, and standard deviation. Qualitative variables were presented as frequency and percentage.

Table 1. Table of results of savings in losses, remnants, and surpluses in a Mixing Center at a tertiary level hospital

January-June 2022				
Medicine number	**Medicine**	**Savings**	**Lost in losses**	**Real savings**
1	AF	$ 7,347.34	$ 1,583.97	$ 5,763.37
2	Z	$ 710.82	$ 599.75	$ 111.07
3	Actinomiycin	$ 128,497.80	$ 29,040.50	$ 99,457.30
4	Bleomicyn	$ 8,745.06	$ 4,425.76	$ 4,319.30
5	Busulfan	$ 679,200.00	$ 294,320.00	$ 384,880.00
6	BV	$ 2,034,081.28	$ 105,026.78	$ 1,929,054.50
7	Carflizomib	$ 733,374.81	$ 147,877.85	$ 585,496.96
8	Carboplatin	$ 34,905.00	$ 2,034.50	$ 32,870.50
9	Cabazitaxel	$ 86,400.00	$ 188,160.00	$ 101,760.00
10	Ciclophosphamide	$ 110,400.00	$ 35,853.00	$ 106,814.40
11	Cisplatin	$ 22,120.04	$ 2,331.38	$ 19,788.66
12	CTRB	$ 125,837.60	$ 813.25	$ 125,024.35
13	Cetuximab	$ 260,341.20	$ 87,518.03	$ 172,823.17
14	Daunorubicin	$ 7,740.00	$ 1,137.14	$ 6,602.87
15	Dexraxozane	$ 52,075.66	$ 29,843.36	$ 22,232.30
16	Dacarbacine	$ 2,530.50	$ 1,491.31	$ 1,039.19
17	Docetaxel	$ 167,134.45	$ 38,924.73	$ 128,209.72
18	Doxorubicin	$ 18,209.26	$ 1,556.13	$ 16,653.13
19	Doxorubicin liposomal	$ 29,385.48	$ 27,671.33	$ 1,714.15
20	Epirubicin	$ 7,737.66	$ 3,120.86	$ 4,616.80
21	Etoposide	$ 9,215.24	$ 358.12	$ 8,857.12
22	Gemcitabine	$ 32,830.00	$ 5,101.72	$ 27,728.29
23	Ifosfamide	$ 39,538.42	$ 2,212.34	$ 37,326.08
24	Irinotecan	$ 13,507.20	$ 2,051.41	$ 11,455.79
25	Mesna	$ 13,036.35	$ 79.61	$ 12,956.74
26	Methotrexate	$ 108,315.00	$ 219.37	$ 108,095.63
27	Mitomycina	$ 1,086.63	$ 374.28	$ 712.35
28	Mitoxantrone	$ 11,374.72	$ 5,829.54	$ 5,545.18
29	Nivolumab	$ 2,698,270.00	$ 245,427.75	$ 2,452,842.25
30	Obinituzumab	$ 308,914.80	$ 2,574.29	$ 306,340.51
31	Paclitaxel	$ 25,875.00	$ 493.89	$ 25,381.11
32	Oxaliplatin	$ 25,875.00	$ 3,547.46	$ 22,327.54
33	Panitumumab	$ 60,820.16	$ 9,883.28	$ 50,936.88
34	Rituximab	$ 450,642.72	$ 32,978.85	$ 417,663.87
35	Trastuzumab	$ 652,955.76	$-	$ 652,955.76
36	Vinblastine	$ 2,587.44	$ 1,336.84	$ 1,250.60
37	VCR	$ 23,263.24	$ 2,144.14	$ 21,119.10
38	5 FU	$ 5,824.00	$ 120.40	$ 5,703.60
Total		$ 9,000,705.64	$ 1,285,795.52	$ 7,714,910.12

Results

A total of 38 oncology medications were evaluated, resulting in a net savings of $9,000,705.64 MXN. Taking into account medication losses, the vial sharing strategy achieved savings of $7,714,910.12 MXN. This cost reduction is particularly significant for high-cost medications such as the anti-PD1 medication Nivolumab, where up to 12 vials of medication can be saved per month, amounting to a savings of $287,050.00 MXN for a single medication. In the case of other antineoplastic agents like carfilzomib, using leftovers can lead to savings of up to 2 vials per month, resulting in savings of up to $93,120.00 MXN. Table 1 resumes the costs and savings data.

With a centralized system, the estimated cost for preparing the 38 medications during the study period was $52,775,243.24 MXN, while the decentralized system cost $61,775,092.01 MXN, resulting in a total savings of $8,999,848.77 MXN with the centralized system in our hospital, representing a cost reduction of 14%.

The vial sharing strategy was effective in reducing costs in the preparation of oncology medications, achieving significant savings. The comparison between the two medication preparation systems demonstrated that the centralized system was more cost-efficient and allowed for a significant cost reduction.

Discussion

The presented study provides valuable insights into the economic impact of implementing a centralized preparation unit and vial sharing strategy in cancer treatment at a tertiary-level hospital in Mexico City. Based on the results, the implementation of the vial sharing strategy and centralized preparation unit could generate significant economic savings in cancer treatment. The findings of this study are consistent with the previous research conducted in similar settings, highlighting the potential for significant economic savings through the adoption of these strategies[13,14].

A study by Johnson et al. examined the implementation of a centralized preparation unit and vial sharing strategy in a large oncology center in the United States. Their findings demonstrated a substantial reduction in medication costs, with estimated savings of over $5 million annually[15]. These results align with our study, suggesting that centralized preparation and vial sharing strategies have the potential to generate significant cost savings across different health-care systems.

Another study conducted by Smith et al. evaluated the economic impact of implementing a vial sharing strategy in a regional cancer center. Their analysis revealed a 25% reduction in medication costs associated with the adoption of vial sharing practices[16]. These findings are similar to the 14% reduction that we observed.

However, it is important to consider some limitations of this study. Being an observational study, a direct causal relationship between the implementation of these strategies and economic savings could not be established[17]. In addition, the study was conducted in a specific hospital, and the results may not be generalizable to other medical centers. Future research should aim to replicate these findings in diverse health-care environments through rigorous comparative studies and randomized controlled trials[18].

The implications of our study are significant for resource management in oncology. By implementing centralized preparation units and promoting vial sharing, health-care institutions can optimize their medication utilization, reduce waste, and achieve substantial cost savings. These strategies not only have the potential to improve cost-effectiveness but also enhance patient care and the sustainability of the health-care system[19,20].

Conclusion

Our study adds to the growing body of evidence supporting the economic benefits of implementing a centralized preparation unit and vial sharing strategy in cancer treatment. By considering the findings from similar studies and addressing the limitations of our research, health-care providers and administrators can make informed decisions regarding the implementation of these strategies. Further research is warranted to explore the generalizability of these findings to diverse health-care settings and to assess their long-term impact on patient outcomes and health-care resource utilization.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of people and animals. The authors declare that no experiments have been carried out on humans or animals for this research.

Data confidentiality. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence to generate texts. The authors declare that they have not used any type of generative artificial intelligence in the writing of this manuscript or for the creation of figures, graphs, tables, or their corresponding captions or legends.

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REVIEW ARTICLE

Gastric cancer and the omics

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Abstract

Gastric cancer is a fatal process whose risk factors include infection by Helicobacter pylori, pernicious anemia, nitroso compounds, alcohol abuse, cigarette smoking, and male gender. Endoscopic surveillance has defined the histological progression of premalignant to malignant lesions. Nevertheless, gastric tumors exhibit distinct histologic variations, clinical behaviors, and treatment responses. This "intra and interpatient heterogeneity" has obliged us to search for key principles governing gastric cancer evolution. Advanced bioinformatics programs, DNA microarray technology, and functional genomics have helped to integrate the structure, function, and dynamics of biological molecules expressed or secreted by cancer epithelial cells that have modified the classification of gastric cancer.

Keywords: *Gastric cancer. Omics classification. GC diversity. Bioinformatics.*

Cáncer gástrico y las ómicas

Resumen

El cáncer gástrico es un proceso fatal cuyos factores de riesgo incluyen la infección por Helicobacter pylori, la anemia perniciosa, la ingesta de compuestos nitrosos, el abuso de alcohol, el tabaquismo y el sexo masculino. El seguimiento endoscópico ha definido la progresión histológica de lesiones premalignas a lesiones malignas. Sin embargo, los tumores gástricos exhiben diferentes y muy variadas variaciones histológicas, comportamientos clínicos y respuestas a tratamiento. Esta gran heterogeneidad intrapaciente e interpaciente ha obligado a la búsqueda de principios reguladores que gobiernen la evolución del cáncer gástrico. Los programas avanzados de bioinformática, la tecnología de microarreglos de ADN y la genómica funcional han ayudado a integrar la estructura, función y dinámica de moléculas biológicas expresadas o secretadas por las células epiteliales cancerosas que han modificado la clasificación del cáncer gástrico.

Palabras clave: *Cáncer gástrico. Clasificación ómicas. Diversidad del cáncer gástrico. Bioinformática.*

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Introduction

Gastric cancer is a leading cause of global cancer morbidity and mortality[1]. It exhibits high levels of histologic, transcriptomic, and epigenomic variation with distinct clinical behaviors and treatment responses[2] but the understanding of gastric tumor biology and the key principles governing gastric cancer evolution are far from being grasped. The Correa Pathway of gastric carcinogenesis describes the histological progression of normal gastric epithelia toward gastric cancer[3] but the emergence of DNA microarray technology and the establishment of functional genomics have modified the classification of gastric cancer. The characterization of this new way to study and integrate structure, function and dynamics of biological molecules has been incorporated in the omics concept. The goal of the omics concept is to screen cell changes involved in cancer hallmarks using techniques such as next-generation sequencing and mass spectrometry techniques. The initial goal is to identify disturbances of genes associated with cell growth control such as oncogenes, tumor suppressor and carekeeper genes, to determine (a) genomic instability whether there are chromosomal balanced structural changes, nonreciprocal structural changes, or altered genetic code of certain genes, or (b) epigenomic instability secondary to DNA methylation-associated to transcriptional silencing of genes and/or activation of oncogenes-, histone modification - that determines gene activation or repression-, or the effect of non-coding RNA whose role depends on their interaction with RNA, or DNA, or protein. Several of these changes to the genetic material can co-occur. Nevertheless, gene regulation in cancer is a hot topic. The branches of research that the concept omics refers to include various biology disciplines that overall try to identify, characterize, and quantify biological molecules that are involved in the structure, function, and dynamics of a cell or a tissue. The objects of study encompass: (1) genomics, the integration of all the disciplines related to the study and application of genomes, (2) epigenomics, the study of the reversible modifications on the genome that affect gene expression without altering the DNA sequence, (3) transcriptomics, the analysis of messengers and non-coding RNA transcripts produced by the genotype at a given time, (4) proteomics, the large-scale study of protein structure and function, (5) metabolomics, the study of the chemical processes involving metabolites, small molecule substrates and intermediates, (6) secretomics, the analysis of all the secreted proteins of a cell, it is considered as a type of proteomics, (7) interactomics, the study of the whole set of molecular interactions in a biological system, (8) metagenomics, the study of the structure and function of entire nucleotide sequences recovered from organisms, (9) lipidomics, the study of the structure, function and interaction of lipid molecules with other lipids and proteins, (10) glycomics, the study of the biological functions of any carbohydrate structure produced by a cell or tissue under specified conditions, and (11) immunomics, the study of the detailed map of immune reactions of a host interacting with a foreign antigen.

Intricacy of histological classifications

As early as 1965 Lauren proposed a histological classification that divides gastric cancer into intestinal type (mainly associated with *H. pylori*), diffuse type, and undetermined type[4]. The incidence of diffuse-type gastric cancer has increased. Nevertheless, gastric cancer is a heterogeneous disease that must be stratified not only by histopathological differences. In 2010, the World Health Organization introduced a classification that recognizes four major histological patterns: tubular, papillary, mucinous, and poorly cohesive, but GC histological classification has followed a tortuous road because anatomical location, tumor size, growth, protrusion, presence of polypoids, and mucosal invasion have been considered in many different classifications[5]. The successful use of cancer genomics programs and transcriptomic analysis has allowed for new gastric cancer classifications and categories beyond their histological definition.

Influence of omics in the classification of gastric cancer

The *Cancer Genome Atlas* considers four molecular subtypes, (1) the Epstein-Barr virus positive (EBV^+), (2) the microsatellite unstable (MI), (3) the genomically stable (GS), and (4) the chromosomal unstable (CIN). The genetic alterations that define the EBV^+ subtype comprise PI3KCA mutation, DNA methylation, PD-L1/2 overexpression and activated immune systems; the hallmarks of the MI subtype are high mutation burden, ARID1A mutation, DNA hypermethylation and activated mitosis, whereas those of the GS subtype are CDH1 and RHOA mutation, Cldn18-ARHGAP fusion, inactivated cell adhesion and histological diffuse type. Finally, the hallmarks for the CIN subtype, which is the most frequent subtype, are TP53 mutation and RTK-RAS amplification. Interestingly most of the poor prognoses diffuse type gastric cancer corresponds to the GS subtype.

The Asian Cancer Research Group (ACRG) has identified four subtypes of gastric cancer linked to distinct patterns of molecular alterations and associated with distinct clinical outcomes: microsatellite-unstable tumors, microsatellite-stable tumors with epithelial-to-mesenchymal transition, microsatellite-stable TP53 positive tumors, and microsatellite stable TP53 negative tumors[6]; P53 activation is based on the detection of the negative regulator CDKN1A and MDM2.

The *Centre for Computational Biology of Duke-National University of Singapore*[7] evaluated the gene expression patterns of gastric adenocarcinomas as they show great heterogeneity expression patterns. The group search for a robust classification of gastric cancer identified three different molecular subtypes with distinctive genomic and epigenomic properties: (1) the proliferative subtype that has high levels of genomic instability, high-level TP53 mutations, and DNA hypomethylation, (2) the metabolic subtype that showed high activity of a pathway associated to the spasmolytic-polypeptide- expressing metaplasia considered as an intermediate in the development of gastric adenocarcinoma and is more sensitive to 5-fluorouracil, and (3) the mesenchymal subtype that contain features of cancer stem cells such as high mRNA levels of N-cadherin, low levels of E-cadherin, activation of transforming growth factor (TGFβ) or vascular endothelial growth factor pathways and are sensitive to PI3K-AKT-mTOR pathway inhibitors. The differences between subtypes were not associated with significant survival variances but the classification might be used to select specific treatments. Interestingly, the comparison of the ACRG and TCGA classifications points to similarities between the different subtypes: MSI with EBV^{+}, MSS/EMT with GS, MSS/$TP53^{-}$ with MSI, and MSS/$TP53^{+}$ with CIN. The analysis of genomic and proteomic data as well as signaling pathways[8] identified two distinct gastric cancer molecular subtypes, (1) the mesenchymal phenotype that shows high genomic integrity, low mutation rates, microsatellite stability and highly activated EMT transition, sensitive to inhibition of IGF1/IGF1R and TGFβ signaling pathways but with markedly poor survival and resistance to standard chemotherapy; interestingly, the diffuse histological phenotype was more common among the mesenchymal phenotype tumors, and (2) the epithelial phenotype that display low genomic integrity but is associated with better survival rates and sensitivity to chemotherapy.

It is worth noticing that in these different gastric cancer subtype classifications there is a great variety of genomic landscapes that derive from the differences in epigenetic mechanisms - DNA methylation, histone modification, noncoding RNAs-or driver gene, such as AR, MYC, or PPARA mutations derived from exposure to pharmaceutical or toxic chemicals, diet, stress, exercise, microbiome, disease exposure, and drug abuse of the different population samples that were analyzed. But it seems that the TGFβ signaling pathway and most importantly, the epithelial-to-mesenchymal process are predominantly affected in all the classifications. Translating proteomic subtyping into clinically proficient early detection markers and/or treatments is an imperative and critical research direction. Table 1 shows some of the main associated genes according to classification.

Genomics and epigenomics

An epigenomic histone modification profile of gastric cancer samples revealed that cancer-relevant gene expression is influenced by enhancer[9] differences in genomic copy number and that HNF4a, a nuclear transcription factor that controls the expression of several genes is a master trans-acting factor associated with cancer heterogeneity[10].

A recent analysis of transcriptomic profiles of primary gastric cancers derived into a consensus mesenchymal-subtype gastric cancer (Mes-GC) classifier[11] where TEAD1 (a transcriptional enhancer factor) is a master regulator of Mes-GC enhancers, especially NUAK1 kinase (a serine/threonine-protein kinase involved in cell proliferation). The results determined that TEAD1 inhibition and combinatorial NUAK1 inhibition/cisplatin represent a therapeutic target.

Proteomics-based classification

Proteomics has been successfully used to classify the diffuse type as the most severe histological type of gastric cancer that has poor clinical outcomes. The gene ontology analysis of gastric cancer tumor proteomics indicated that the altered genes were significantly enriched in EMT, cell cycle, DNA replication, p53 signaling, and inflammatory response pathways whereas normal nearby tissue was enriched with fatty acid metabolism, oxidative phosphorylation, and amino acid metabolism pathways. The use of consensus clustering methodology helped in the identification of three different subtypes based on differentially expressed proteins and distinctive pathway enrichment and clinical outcome: (1) the PX1 cluster that exhibits dysregulation in the cell cycle, (2) the PX2 cluster that

Table 1. Genes associated with histologically/molecular classified subtypes

Classification	Subtype	Major associated genes
Lauren	Intestinal	FUT, LGALS4, CDH17
Lauren	Diffuse	AURKB, ELOVL5
Lei	Proliferative	Decreased TP53 mutations
Lei	Metabolic	Increased TP53 mutations
Lei	Mesenchymal	Increased TP53 mutations
*CGA	EBV- positive	PIK3CA, JAK2, PDL1/2, BCOR
*CGA	Microsatellite instable	PIK3CA, ERBB2/3, EGFR, PDL1, MLH1, TP53
*CGA	Genomic stable	CDH1, RHOA
*CGA	Chromosomal unstable	SMAD4, APC, TP53, RTK-RAS
**ACRG	Microsatellite unstable high	ARID1A, MTOR, KRAS, PIK3CA, ALK, PTEN
**ACRG	Microsatellite stable/Epithelial-mesenchymal transition	CDH1
**ACRG	Microsatellite stable/TP53+	APC, ARID1A, KRAS, PIK3CA, SMAD4
**ACRG	Microsatellite stable/TP53-	ERBB2, EGFR, CCNEI, CCND1, MDM2, ROBO2, GATA6, MYC

*CGA: cancer genome atlas; **ACRG: Asian cancer research group

on top of the dysregulation of the cell cycle features an additional epithelial-to-mesenchymal process, and (3) the PX3 cluster that is enriched in immune response proteins, has the worst survival and is insensitive to chemotherapy.

The intent to reproduce molecular classifications using immunohistochemical analysis and in situ hybridization has proved to be useful as the results have corroborated the effectiveness of this approach. The results show that the evaluation by both methods of EGFR, HER2, TP53, EBV, E-cadherin, MLH1, and microsatellite instability help to classify biological and clinically different gastric cancer subgroups. The relevance of using immunohistochemistry to complement omics analysis has been established. Using a similar approach subset within the defined molecular subtypes has been identified. Like claudin-6, a protein not expressed in normal gastric epithelia and strongly associated with greater gastric cancer invasiveness and metastatic capacity[12] which has been proposed as a subcategory of the CIN molecular subtype of gastric cancer. CIN gastric cancer overexpressing claudin-6 show higher mutations in TP53, MIEN1, STARD3, PGAP3, CCNE1, MAGEA9b, and APOA2 genes[13].

The great genomic diversity found that in gastric cancer bioinformatics analysis is further exemplified by particular analysis of signaling and metabolic pathways made considering a single protein for example claudin 6 high expression where the main major disrupted pathways are complement and coagulation cascades (3.3-23), cholesterol metabolism (1.9-12), fat digestion and absorption (1.8-7), and many others[13].

Secretomics-based classification

The latest comprehensive multi-omic analysis of gastric cancer malignant ascitic fluid samples classification stratified ascites-disseminated gastric cancer metastases into two distinct molecular subtypes: one displaying active super-enhancers at the ELF3, KLF5, and EHF loci, and a second where the transcriptional enhancer factor TEF-1 is highly expressed and TGFβ pathway is activated through SMAD3 (Table 1)[14].

Despite differences in histology and outcomes between the intestinal and the diffuse subtypes proteomic and phosphoproteomics analysis allowed the identification of specific signatures between both subtypes[15]. A total of 4,846 proteins were identified in the diffuse type, interestingly 255 were overexpressed and 372 were underexpressed, whereas in the intestinal subtype, a total of 7,448 proteins were identified but only 15 were overexpressed and 56 were underexpressed; a further pathway analysis showed that a canonical pathway that favors the accumulation of acetaldehyde,

associated to gastric cancer development due to its effect on the DNA, was the most involved in the intestinal subtype. *H. pylori* infection is mainly associated with the intestinal subtype because of its enhanced production of acetaldehyde.

Phosphoproteomics

The analysis of phosphorylated amino acid residues in proteins from biological species has evolved as kinase inhibition is now involved in cancer therapy. Gastric cancer phosphorylation landscapes have elucidated signaling pathways associated with somatic mutations based on mutation-phosphorylation correlations[16]. The phosphorylation landscape of 28,000 diffuse gastric cancer phosphorylation sites identified 445 upregulated phosphorylated sites associated with cell-cycle pathways cell-cell adhesion, DNA repair and mRNA splicing pathways but consensus clustering identified three clusters, Ph1, Ph2, or Ph3, associated with distinct clinical outcomes[17]. The Ph1 subtype showed upregulated rRNA processing and RNA polymerase II promoter activity, the Ph2 subtype upregulated DNA metabolism and DNA repair but lost gastric acid secretion, the Ph3 subtype upregulated chromosome segregation and lost cell-cell interaction and communications.

Glycomics

Analyze the structure and function of glycans in biological systems. O-glycan alterations in gastric cancer tissue are the result of glycosyltransferases accessibility and/or availability of sugar-nucleotide precursors amongst many others. Altered glycosylation is a hallmark of malignant transformations that contributes to disease outcomes[18]. Aberrant glycosylation including an increase in overall sialylation of sialyl Lewis x and sialyl Lewis a antigen as well as an increase in terminal a2,6-sialylated structures in truncated O-linked and N-linked glycans has been reported in many different cancers. The same modifications are reported in gastric cancer although the differences can not specifically differentiate between subtypes[19] some reports indicate that mucin-associated sialylated antigens Sialyl Lewis^{a} $^{and\ x}$, as well as Sialyl Tn expression in the diffuse subtype, have a worse prognosis[20].

Secretomic and immunomics analysis has helped untangled the complexities of tumor microenvironments. It has long been recognized that cancer and stromal cells, mainly fibroblasts, interact in the cancer microenvironment by secreted proteins (TGFβ, PDGF, FGF-2) through autocrine and paracrine pathways. The analysis of the functional secreted molecules involved in gastric cancer showed that the secretion of growth and differentiation factor 15 (GDF15), a molecule only expressed in fetal tissue and placenta, is significantly higher in the diffuse subtype gastric cancer[21,22]. GDF15 has an immunoregulatory function and it is now considered as an immune checkpoint thus becoming a target for cancer immunotherapy. The FGFR1 and 2 proteins are overexpressed in the diffuse gastric cancer subtype and are associated with tumor progression and peritoneal dissemination[23]. The analysis of proteins contained in exosomes secreted by cancer cells revealed that insulin receptor signaling affects tumor cell invasion as it modulates E-cadherin glycosylation thus increasing the expression of mesenchymal markers[24]. More recently, the secreted Interleukin-1 receptor accessory protein has been defined as relevant as its expression is significantly increased in successive stages of gastric adenocarcinoma[25]. Immune infiltration analysis in the tumor microenvironment has identified two subtypes of cancer: immunological hot and cold; these different phenotypes are relevant to the therapeutic response to immune checkpoint inhibitors[26]. This type of analysis in gastric cancer demonstrated that the overexpression of the tight junction protein claudin 3 in the “cold” tumors is associated with inhibition of MHC-1 and CXCL9 expression and poor infiltration of CD8+ T cells[27].

Microbiomics

Despite the progress in the identification of specific factors contributing to gastric carcinogenesis (genes, proteins, metabolic molecules, and pathways, sensitivity to immune effectors), there is ample evidence suggesting that the gut microbiome can foster epigenetic alterations and mutagenesis on the host genome and impact responses to cancer therapy, especially by influencing the response to immune checkpoints blockade[28]. The preservation of the spatial relationship between microbiota and the epithelial surface is essential to avoid harmful immune responses but it is regulated by functional oscillations in the metabolome patterns that determine the exposure of the epithelium to different bacterial species and their metabolites[29]. When commensal bacteria are disrupted the consequent dysbiosis can lead to impaired local, regional and systemic immune responses that incite a profound inflammatory state[30]. Niche-specific microbiota

alterations have been reported during the progression from gastritis to gastric cancer although *H. pylori* mainly affected the gastric corpus microbiota and not the gastric antrum. Similarly, gastric cancer-specific stomach peritumoral and tumoral microhabitats determine the composition and diversity of the gastric microbiota[31] which is composed mainly by *Firmicutes*, *Bacteriodetes*, *Actinobacteria*, *Fusobacteria,* and *Proteobacteria*. Interestingly a low gastric microbial dysbiosis and distinct dietary patterns-vegetable and seafood in males and high dairy consumption in females- reduce the gastric cancer risk[32]. The major bacterial metabolites associated with gastric cancer development are polyamines, N-nitroso compounds, and lactate which play a role in immune escape and suppressing the antitumor immunity[33]. Metatranscriptomic analysis of the gastric microbiota in human corpus premalignant tissue demonstrated *H. pylori* abundance and high expression of genes involved in pH regulation (urea and ureB), nickel availability (hpn and hpn2) and oxidative damage protection (katA, trxA, tsaA, fldA, and sodB)[34]. Nevertheless, recent evidence suggests that gastric dysbiosis imbalance after *H. pylori* eradication may be associated with gastric cancer development[35].

Can system vaccinology be considered as an omic?

Omics analysis has helped in the identification of dysregulated genes, epigenetic abnormalities, altered transcription mechanisms, affected cellular pathways, overexpressed or atypical proteins and/or receptors, and modified sugar-lipid-amino acids metabolites, associated with gastric carcinogenesis. All of them have been evaluated as possible biomarkers of early detection, tumor subtype, prognosis, and survival probability but an essential question remains can we produce long-term protection against the development of gastric cancer? Can all this information lead to a protective vaccine?

The integration of all the omics has favored the identification of potentially new antigens that have been used to generate a vaccine against several solid tumors[36]. The advent of high-throughput technologies coupled with systems biological methods, an approach to understanding the larger picture of tissues or cells, has enabled the characterization the identification of predictive signatures of vaccine response. The latter, known as systems vaccinology[37], coupled with cytometry analysis and its integration with omics information will certainly be applicable for vaccine development[38].

Perspectives

So far, the major advances in high-throughput omics methodologies have been the discovery of mechanisms involved in vaccine protection, immune memory, secondary effects, and mostly the development of more efficient antigens.

Overall a comprehensive overview of the reported associations between DNA variations showed that genetic variants significantly associated with the risk of gastric carcinoma were associated with cell signal transduction (IGFBP3, PLCE1, PPARG, and PRKAA1), cell adhesion (ABO, MUC1, THBS3, and TIMP2), cell apoptosis/proliferation (CASP8, MDM2, MTX1, TP53, and PSCA), cell metabolism (EPHX1, GSTP1, and PKLR), and immunity/inflammation (IL-1b, IL-8, IL-10, IL-17F, TGFβR2, TNF, TLR4, and PTGS2). These results suggest that the exploration for gastric cancer-specific genes is subject to genetic variations affecting different populations so its usefulness as diagnostic biomarkers could be considered as restricted.

So far, the most commonly clinically available biomarkers of gastric cancer include CEA, CA19-9, CA72-4, AFP, CA125, and HER2 but due to their poor specificity and sensitivity, their use as dependable tumor biomarkers is limited. The current evaluation of Fibroblast Growth Factor Receptor 2, E-cadherin, Akt, PDL1, MET, VEGFR2, TP53, and Claudin-6[39-44] have proved to be of more clinical value than the comprehensive genomic analysis for the early diagnosis and prognosis of gastric cancer[45]. We strongly believe that an evaluation of the possible abnormalities accompanying each of the different cell populations that constitute the gastric epithelial could help in the understanding of the vast differences observed in the histology and the omics of gastric cancer.

Conclusion

Although the conceptual pathway for gastric cancer vaccine development is clear and the use of bioinformatic analysis embraced in the omics concept has provided important tools to understand the biology of gastric cancer and the regulatory role that the tumor microenvironment exerts, we are a long distance to achieve our main goal, that is, to diagnose gastric cancer in the early stages based on detection of specific genes and to treat patients with specific pathways inhibitors and/or immune suppressors.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

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CONSENSO

Consenso mexicano de cáncer mamario. Manejo del cáncer de mama avanzado

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Resumen

El cáncer de mama es la neoplasia más frecuente y con mayor mortalidad en mujeres en todo el mundo. La décima actualización del Consenso Mexicano Sobre Diagnóstico y Tratamiento del Cáncer Mamario (2023) es publicada por sus autores en diferentes artículos. El presente artículo incluye el manejo de cáncer de mama avanzado, el tratamiento sistémico adyuvante, el papel de la cirugía y la radioterapia en enfermedad metastásica y el seguimiento posterior al tratamiento con intención curativa. La difusión de este consenso contribuye a la actualización y homogeneidad de criterios de manejo del cáncer mamario en etapas avanzadas.

Palabras clave: *Cáncer de mama. Metástasis. Consenso.*

Mexican breast cancer consensus. Management of advanced breast cancer

Abstract

Breast cancer is the most common neoplasia, with the highest mortality in women worldwide. The tenth update of the Mexican Consensus on Diagnosis and Treatment of Breast Cancer (2023) is published by its authors in different articles. This article includes the management of advanced breast cancer, the adjuvant systemic treatment, the role of surgery and radiotherapy in metastatic disease, and follow-up after treatment with curative intent. The dissemination of this consensus contri-butes to the updating and homogeneity of breast cancer management of advanced stages.

Keywords: *Breast cancer. Metastatic. Consensus.*

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Introducción

El cáncer de mama metastásico es una enfermedad heterogénea, con manifestaciones clínicas variables y cuyo tratamiento depende del sitio y el número de las metástasis, las características de la paciente, el inmunofenotipo tumoral y la sensibilidad o la resistencia a los tratamientos médicos oncológicos previos[1].

En esta etapa de la enfermedad se ha observado una mejoría importante en la mediana de supervivencia, con rangos muy variables, dependiendo del inmunofenotipo[2-4].

Las metas del tratamiento en el cáncer mamario metastásico son:

- Prolongar el intervalo libre de progresión y la supervivencia global (SG).
- Paliar los síntomas relacionados con la enfermedad.
- Mantener una adecuada calidad de vida con buen estado funcional.

Los factores clínico-patológicos más importantes para decidir la mejor estrategia terapéutica son[1,3]:

- Edad.
- Síntomas relacionados con la enfermedad y el estado funcional.
- Enfermedades concomitantes.
- Intervalo libre de enfermedad.
- Número y localización de metástasis.
- Tratamiento previo y respuesta a este.
- Receptores hormonales (RH), *HER2* neu, mutaciones de *BRCA* 1 y 2 y expresión del ligando de muerte programada 1 (PD-L1) (solo en triple negativo).
- Preferencias de la paciente.

En pacientes con etapas I a III y que posteriormente presentan recurrencia tumoral, se recomienda la evaluación de la extensión de la enfermedad metastásica incluyendo realizar una biopsia de un sitio metastásico para confirmar el diagnóstico y determinar el estado de RH y *HER2*, ya que se ha demostrado que hasta en un 30% de los casos cambia su inmunofenotipo[5]. También se recomienda evaluar la presencia de mutaciones germinales de *BRCA* 1 y 2 y la expresión de PD-L1 (solo en triple negativo) en vista de disponer de opciones terapéuticas aprobadas[6,7]. No se recomienda realizar otros biomarcadores.

El tratamiento se establece de acuerdo con el subtipo de cáncer de mama:

- Cáncer de mama metastásico/recurrente con RH positivos *HER2* negativo.
- Cáncer de mama metastásico/recurrente con RH positivos *HER2* positivo.
- Cáncer de mama metastásico/recurrente con RH negativos *HER2* positivo.
- Cáncer de mama metastásico/recurrente triple negativo o con RH positivos *HER2* negativo no candidatas a hormonoterapia (*BRCA* positivo/negativo).

Tratamiento sistémico

Cáncer de mama metastásico con receptores hormonales positivos y HER2 neu negativo

La terapia endocrina más un inhibidor de CDK4/6 es el tratamiento de elección, debido a que se ha demostrado incremento de SG, tanto en primera como en segunda línea de tratamiento[8], además de mejoría de otros parámetros de eficacia, como supervivencia libre de progresión y tasas de respuesta, incluyendo pacientes con enfermedad visceral. Sin embargo, en las pacientes con síntomas importantes y/o metástasis viscerales de progresión rápida (crisis visceral)[1] se recomienda quimioterapia como una opción debido a que produce mayores porcentajes de respuesta. La crisis visceral es una disfunción orgánica grave representada por síntomas y signos, estudios de laboratorio y enfermedad rápidamente progresiva. La crisis visceral no se refiere exclusivamente a la presencia de metástasis viscerales, sino que implica compromiso visceral significativo que obliga a una terapia eficaz y de acción rápida, en particular si otra opción de tratamiento después de una ulterior progresión no es posible.

Para la toma de decisiones terapéuticas en este apartado es importante tomar en consideración los siguientes conceptos[1]:

- Resistencia endocrina primaria. Considerada para pacientes con recurrencia dentro de los primeros dos años de terapia endocrina adyuvante o progresión de la enfermedad, dentro de los primeros seis meses de la primera línea para enfermedad metastásica.
- Resistencia endocrina secundaria. Definida como recurrencia durante terapia endocrina adyuvante, después de los dos primeros años, recurrencia después de 12 meses de haber completado hormonoterapia adyuvante o progresión de la enfermedad en el contexto de enfermedad metastásica, posterior a seis meses de haber iniciado primera línea.

Tratamiento hormonal en pacientes premenopáusicas

Debido a los beneficios de la terapia endocrina + otras terapias blanco en pacientes posmenopáusicas, se recomienda la ablación ovárica médica o quirúrgica en pacientes premenopáusicas, y tratarlas como posmenopáusicas[1].

Un inhibidor de aromatasa más ribociclib, con ablación o supresión ovárica, está indicado como tratamiento de primera línea en pacientes premenopáusicas[9].

El tamoxifeno como monoterapia es una opción en las pacientes que no acepten la supresión o ablación ovárica.

Tratamiento hormonal en pacientes posmenopáusicas

Primera línea

En pacientes con enfermedad metastásica *de novo* o enfermedad recurrente con resistencia endocrina secundaria, el tratamiento estándar es inhibidor de aromatasa + un inhibidor CDK4/610-13. Actualmente en México se dispone de palbociclib, ribociclib y abemaciclib; el ribociclib es el único inhibidor CDK4/6 que hasta el momento ha demostrado incrementar la SG[10-14]. Sin embargo la elección del tratamiento debe considerar también la edad, el estado funcional, las comorbilidades, el perfil de toxicidad, la disponibilidad y las preferencias del paciente.

Un inhibidor de la aromatasa (IA) es también una opción en pacientes para las que no se tenga disponibilidad de inhibidores CDK4/6[15].

Otra posibilidad adicional de primera línea es el fulvestrant, principalmente en pacientes con ausencia de metástasis viscerales[16].

Segunda línea

Si las pacientes ya recibieron un IA no esteroideo (anastrozol/letrozol) o presentan progresión durante el tratamiento adyuvante con IA no esteroideo, la primera opción de tratamiento es:

- Fulvestrant más inhibidor CDK4/6 (palbocicib, ribociclib o abemaciclib), siempre y cuando no se hubiera usado este último en la primera línea[14-20].

Otras opciones:

- Exemestano más everolimús[21,22].
- Exemestano[22,23].
- Fulvestrant[24].
- Fulvestrant más everolimús[25].

Tercera línea

La tercera línea dependerá de la primera y segunda líneas recibidas. Hasta el momento no existe una secuencia estándar.

Abemaciclib monodroga es una opción de tratamiento de tercera línea, en pacientes que no han recibido inhibidor CDK4/6 en líneas previas, ya sea con tratamiento endocrino o quimioterapia[26].

De estar disponible, trastuzumab/deruxtecán es una opción de tercera línea en pacientes con RH positivos y *HER2* neu bajo (definido con escala 1 + o 2 ++ por inmunohistoquímica y con hibridación *in situ* negativa)[27].

En las pacientes con respuesta o claro beneficio clínico inicial con hormonoterapia y que progresan con una primera línea, deberá intentarse una segunda, tercera e incluso cuartas líneas hormonales dependiendo del fármaco utilizado previamente, dado que a menudo se obtiene de nuevo respuesta tumoral, lo que significa la posibilidad de supervivencia libre de quimioterapia, con mejor calidad de vida. En caso de resistencia comprobada al manejo hormonal, deberá cambiarse a quimioterapia.

Para las pacientes con receptores positivos que hayan recibido quimioterapia hasta el máximo beneficio se sugiere continuar con hormonoterapia de mantenimiento y el fármaco elegido se administrará hasta la progresión[1].

Cáncer de mama metastásico/recurrente con receptores hormonales positivos y *HER2* neu positivo (triple positivo)

El tratamiento recomendado es la quimioterapia asociada a terapia anti-*HER2* debido al incremento en la SG demostrado (ver sección de Cáncer de mama metastásico/recurrente con receptores hormonales negativos y HER-2 neu positivo)[1,28].

En pacientes con respuesta completa y/o que presentan una toxicidad limitante de dosis, es posible suspender la quimioterapia y continuar con el bloqueo anti-*HER2* en combinación con terapia endocrina (monodroga)[1].

En pacientes posmenopáusicas no candidatas a quimioterapia, con alta expresión de RH, *de novo* o con un periodo libre de enfermedad largo y ausencia de enfermedad visceral, podría utilizarse el doble bloqueo anti-*HER2* (trastuzumab/lapatinib o pertuzumab/trastuzumab) en combinación con un inhibidor de aromatasa no esteroideo, esta estrategia demostró un beneficio en sobrevida libre de progresión (SLP), pero no en SG. La terapia anti-*HER2* (trastuzumab o lapatinib) con terapia endocrina es otra alternativa, considerando que tiene una mediana de SLP menor[29-32].

Cáncer de mama metastásico/recurrente con receptores hormonales negativos y *HER2* neu positivo

Para decidir el manejo es importante estratificar a los pacientes con base en la exposición previa a terapias

anti-*HER2* y el tiempo transcurrido entre la última dosis de terapia anti-*HER2* y la recurrencia o progresión de la enfermedad[28].

Primera línea

El tratamiento estándar para pacientes en etapa IV *de novo* o expuestos a terapia anti-*HER2* durante la neo/adyuvancia y con más de 12 meses de SLE, es docetaxel o paclitaxel en combinación con un doble bloqueo anti-*HER2* basado en trastuzumab y pertuzumab, ya que ha demostrado claramente un beneficio en la SG, la supervivencia libre de progresión y la tasa de respuestas[33,34].

En pacientes que no pueden recibir pertuzumab debe considerarse la combinación de trastuzumab más taxano o vinorelbina como una alternativa[35,36].

Si un paciente expuesto a terapia anti-*HER2* durante la neo/adyuvancia presenta progresión de la enfermedad durante el tratamiento o en un periodo menor a seis meses de finalizada su última dosis, es recomendable utilizar trastuzumab/deruxtecán o en ausencia pertuzumab y trastuzumab emtansina (T-DM1)[37,38].

Segunda línea y posteriores

No se recomienda el uso de pertuzumab más allá de la progresión a la primera línea de tratamiento[39].

En pacientes previamente tratadas con un esquema basado en trastuzumab y con progresión de la enfermedad, el tratamiento indicado es trastuzumab/deruxtecán o en ausencia T-DM1[37,38].

En pacientes que no pueden recibir trastuzumab/deruxtecán o T-DM1, debe considerarse la opción de continuar con trastuzumab en combinación con un agente de quimioterapia. Los esquemas mencionados previamente y el doble bloqueo con trastuzumab/lapatinib pueden ser utilizados en tercera línea y subsecuentes de forma indistinta[39,40].

En todas las pacientes se recomienda mantener el bloqueo con terapia anti-*HER2* durante todas las fases del tratamiento antineoplásico, excepto en los casos en que esté contraindicado, ya que está demostrado su impacto en el control de la enfermedad[28,41-43].

Cáncer de mama metastásico/recurrente triple negativo o con receptores hormonales positivos *HER2* negativo no candidatas a hormonoterapia (*BRCA* positivo/negativo)

En todas las pacientes con cáncer de mama triple negativo se debe realizar de forma sistemática la determinación de variantes patogénicas germinales de *BRCA*, así como determinación de PD-L1[44].

La elección del tratamiento debe tomar en cuenta la terapia adyuvante previa (Tabla 1) y el intervalo libre de recurrencia. En pacientes con un intervalo mayor de un año es posible evaluar la reinducción de fármacos. Para pacientes con tumores triple negativo, una opción de tratamiento es la quimioterapia, sin que sea posible recomendar en la actualidad un esquema o secuencia específicos[1,44,45]. Los estudios que evaluaron el uso de pembrolizumab más quimioterapia o sacituzumab/govitecán demostraron una mayor eficacia e incremento en la SG *vs.* quimioterapia[46,47].

Quimioterapia de primera línea: ¿en combinación o secuencial?

No se recomienda poliquimioterapia de forma estándar. Se prefiere el tratamiento con fármacos como monodroga y de forma secuencial, debido a su mejor tolerancia y menor deterioro en la calidad de vida. El uso de poliquimioterapia puede ser considerado en pacientes con buen estado funcional en las que se busca una rápida respuesta o paliación de síntomas y/o en caso de crisis visceral y/o en los casos en que se considere que la expectativa de vida solo permite una oportunidad de tratamiento[1,38,48,49].

La piedra angular de la quimioterapia de primera línea se basa en antraciclinas y taxanos. En pacientes previamente expuestas, las opciones de tratamiento incluyen: capecitabina, gemcitabina, vinorelbina o eribulina (Tabla 1).

En caso de que se elija una combinación se recomienda un taxano (paclitaxel o docetaxel) más capecitabina o gemcitabina. Ambos esquemas se han asociado con mayores tasas de respuestas e intervalo libre de progresión vs. taxano como monodroga[49-55]. La eficacia de ambos esquemas es similar y la elección dependerá de las características de cada paciente y los recursos disponibles.

El nab-paclitaxel está indicado en pacientes con falla a una línea previa de quimioterapia en el contexto de enfermedad metastásica o contraindicación a paclitaxel. En el caso de elegir paclitaxel, se recomienda de forma semanal[56,57]. Nab-paclitaxel está indicado en pacientes con falla a un esquema previo de quimioterapia en el contexto de enfermedad metastásica o en pacientes con contraindicación a paclitaxel[58]. La eribulina es

Tabla 1. Cáncer de mama metastásico triple negativo o con receptores hormonales positivos, HER2 neu negativo no candidato a hormonoterapia

Adyuvancia				
	No recibió	**Con taxano+antraciclina**	**Con taxano**	**Con antraciclina**
1.ª línea	Esquema basado en: Antraciclina Taxano*	Capecitabina Eribulina Gemcitabina Vinorelbina Sales platinadas†	Esquema basado en: Antraciclina	Taxano ± Capecitabina Gemcitabina
2.ª línea	De acuerdo con el tratamiento utilizado previamente			
3.ª línea	De acuerdo con el tratamiento utilizado previamente			

*Se incluye docetaxel, paclitaxel y nab-paclitaxel.
†Solo en tumores triple negativos.

el único fármaco que ha demostrado impacto en SG en pacientes previamente tratados con taxanos/antraciclinas en población con tumores triple negativo[59,60].

La elección del tratamiento depende de las características de las pacientes, la tolerancia y respuesta a tratamientos previos, así como de la disponibilidad[1,44].

Sales de platino

Existen estudios que muestran la efectividad del platino y sus derivados en tumores triple negativo[59-62]. El estudio TNT, un ensayo fase III, evaluó el uso de docetaxel *vs.* carboplatino y mostró no superioridad de la sal platinada. En población triple negativa no seleccionada (*BRCA* mutación germinal vs. mutado), sin embargo, en la población con mutación germinal *BRCA* presente se observó una superioridad en la supervivencia libre de progresión a favor de carboplatino[62]. Aunque las sales de platino no se recomiendan como terapia de primera línea en población no seleccionada, puede representar una opción en población con mutación germinal de *BRCA*[61-63].

Bevacizumab

El uso de bevacizumab más un agente de quimioterapia incrementa el control de la enfermedad y la supervivencia libre de progresión, pero no impacta en la SG como terapia de primera línea en cáncer de mama metastásico[64-69]. Es una opción de tratamiento utilizar bevacizumab más taxano en pacientes con tumores triple negativo o en aquellas con RH positivos, que cursan con una evolución clínicamente agresiva y se consideran candidatas a quimioterapia de primera línea.

Inmunoterapia

Pembrolizumab más quimioterapia (paclitaxel, nab-paclitaxel o gemcitabina más carboplatino) en pacientes con cáncer de mama triple negativo avanzado que expresan PD-L1 (puntuación positiva combinada [CPS] > 10%/clona IHC 22C3 pharmDx), como terapia de primera línea demostró ser superior vs. quimioterapia en SG y supervivencia libre de progresión[7,46].

Inhibidores de la poli(ADP)-ribosa polimerasa (PARP)

En pacientes con cáncer de mama y variantes patogénicas germinales de *BRCA*, el olaparib y el talazoparib demostraron impacto en la supervivencia libre de progresión, por lo que pueden ser considerados una opción de tratamiento[70-72].

Anticuerpos conjugados

Sacituzumab/govitecán

En pacientes con cáncer de mama metastásico previamente tratadas, el uso de sacituzumab/govitecán incrementó la supervivencia libre de progresión y SG, por lo que debe ser considerado una opción de tratamiento[47].

Trastuzumab/deruxtecán

En pacientes con cáncer de mama metastásico previamente tratadas, con expresión con *HER2* baja y RH negativos, está indicado el uso de trastuzumab/deruxtecán[27].

Duración del tratamiento

La duración del tratamiento no se ha definido por completo. Varios estudios han demostrado que continuar la quimioterapia puede incrementar el intervalo libre de progresión, pero sin prolongar la supervivencia[73,74].

En la práctica clínica se recomienda continuar la quimioterapia hasta la progresión o toxicidad, dependiendo del fármaco aplicado (intravenoso frente a oral), las dosis máximas acumuladas y el impacto en la calidad de vida de las pacientes.

Bisfosfonatos e inhibidores del ligando del receptor activador del factor nuclear kB (RANKL) en metástasis óseas

Tanto los bisfosfonatos como los inhibidores del ligando del receptor activador del factor nuclear kB (RANKL) permiten mejorar los resultados en el manejo de las metástasis óseas, la hipercalcemia maligna y la salud ósea al reducir la osteopenia u osteoporosis secundarias al tratamiento sistémico[73-77].

Los pacientes con evidencia radiográfica de metástasis óseas deben recibir tratamiento, ya sea con denosumab (120 mg subcutáneo cada 4 semanas)[79] o con ácido zoledrónico (4 mg por vía intravenosa en 15 minutos) cada tres a cuatro semanas[78-81].

- La duración total del tratamiento con bisfosfonatos debe ser hasta de dos años.
- El ácido zoledrónico puede aplicarse cada tres a cuatro semanas o cada tres meses, desde un inicio[82].
- Después de un año de tratamiento y en caso de enfermedad estable, se recomienda la administración de ácido zoledrónico cada 12 semanas durante el segundo año[83] y después reconsiderar su uso según la actividad de las metástasis óseas.
- No se conoce la duración óptima del tratamiento con denosumab.

Las recomendaciones generales con el uso de bisfosfonatos e inhibidores de RANKL son las mismas que en adyuvancia.

Papel de la cirugía en enfermedad metastásica

El tratamiento estándar del cáncer de mama en estadio IV se enfoca en todos sus escenarios posibles hacia un terreno paliativo, en el cual se incluye quimioterapia, radioterapia, terapia hormonal, inmunoterapia y terapias blanco, dejando el papel de la cirugía solo para prevención o tratamiento de síntomas locales[84], sin embargo en los últimos 20 años diversos centros en todo el mundo han publicado series de pacientes con cáncer de mama metastásico que experimentaron resección en varios sitios (hígado, cerebro, pulmón), reportando resultados favorables[85] principalmente en aquellas con metástasis al momento del diagnóstico. De hecho, la mediana de SG del cáncer de mama metastásico casi se ha triplicado de 13 meses en 1985 a 33 meses en 2016, gracias al tratamiento multimodal[86,87]. En contraste, en 2022 se publicaron los resultados del protocolo NCT02364557, en donde se demostró que la adición de terapias locales al manejo sistémico no mejoró el periodo libre de enfermedad ni la SG en pacientes con enfermedad metastásica, incluso con patología oligometastásica[88].

Resección de enfermedad metastásica

Metástasis hepáticas

El hígado representa, como único sitio de metástasis a distancia, solo el 10% de los casos, por lo que la resección hepática ha tenido un papel limitado en el tratamiento, ya que lo más frecuente es que se acompañen de metástasis a otro nivel[89]. Se ha reportado que la tasa de supervivencia a cinco años después de la resección quirúrgica de las metástasis hepáticas, combinado a la terapia sistémica, oscila entre el 40 y el 61%. Las técnicas quirúrgicas actuales permiten que la resección tenga una mortalidad postoperatoria inferior al 6% y una morbilidad entre el 0.8 y el 5.4% en centros de referencia[90]. Otra opción válida es utilizar ablación de las metástasis con radiofrecuencia o con termoterapia intersticial inducida con láser, con lo que se reporta supervivencia media de 30 a 60 meses y supervivencia a cinco años del 27 al 41%[90].

En relación con factores pronósticos, la mayoría de los estudios enfatiza la importancia de la resección R0, ya que el margen positivo es un factor adverso para la supervivencia[91]. Otros factores predictores adversos para la supervivencia han sido el tamaño de las lesiones (> 5 cm), el estatus de los RH negativos, pobre respuesta a la quimioterapia, la invasión vascular, el número de metástasis y el intervalo libre de enfermedad menor a un año después de la resección primaria de cáncer de mama[92].

Metástasis pulmonares

La enfermedad metastásica es frecuentemente generalizada y en pocas ocasiones está solo localizada

a nivel pulmonar. En una serie de 13,502 pacientes con cáncer de mama en la Clínica Mayo se encontraron apenas 60 (0.4%) con metástasis pulmonares aisladas, de los cuales 40 fueron llevados a cirugía[93].

La resección quirúrgica completa de metástasis pulmonares puede realizarse con morbilidad y mortalidad bajas, ya sea realizada por toracotomía o por cirugía toracoscópica asistida por video. El análisis de series de casos ha establecido los siguientes criterios de selección quirúrgica bien aceptados:

- La enfermedad primaria está bajo control.
- Metástasis limitadas al pulmón y pleura.
- Capacidad de extirpar por completo la enfermedad metastásica (R0).
- Reserva fisiológica pulmonar para tolerar el procedimiento planificado[94].

Un hallazgo común en la mayoría de los estudios que evalúan el papel de la resección de las metástasis pulmonares es que el intervalo libre de enfermedad, entre el manejo inicial del primario y la aparición de metástasis pulmonares, impacta muy significativamente en la supervivencia. El intervalo libre de enfermedad de más de 36 meses a la recurrencia ha logrado supervivencias a cinco años de hasta el 75% en lesiones únicas llevadas a resección y tratamiento sistémico[95].

Otros factores asociados con mejoría de la supervivencia han sido los RH positivos, *HER2* neu positivo y metástasis solitarias. Como en el caso de las metástasis hepáticas, las pacientes con lesiones únicas e intervalo libre de enfermedad prolongado deben considerarse candidatas a metastasectomía pulmonar.

Metástasis cerebrales

El cáncer de mama representa la segunda causa de lesiones metastásicas en el cerebro y generalmente están asociadas a tumores con RH negativos, *HER2* positivo, pacientes premenopáusicas y con enfermedad metastásica en pulmón y/o hígado[96]. Las pacientes que no reciben ningún tipo de tratamiento tienen un pronóstico de supervivencia de uno a dos meses, la cual se incrementa hasta seis meses en las que reciben radioterapia y cuando está indicada la cirugía puede incluso llegar hasta 16 meses[97].

Las indicaciones de la cirugía son limitadas, siendo una opción razonable en lesiones únicas, tamaño < 5 cm, ausencia de metástasis extracraneales y sobre todo pacientes con adecuado estado funcional. La resección paliativa de estas lesiones está indicada para mejorar los síntomas que presente la paciente o como urgencia para mantener la vida de esta.

Otros sitios metastásicos

Este grupo es menos estudiado y en general no ha mostrado beneficio en la supervivencia. Un ejemplo es el de las metástasis óseas; según varios reportes, en esas pacientes la resección quirúrgica no ha mostrado mejoría en el pronóstico[98], siendo la radioterapia la modalidad paliativa de elección. Por otra parte, algunos estudios han reportado que la resección de metástasis en esternón o caja torácica se asocia con incremento de la supervivencia[99]. Menos estudiadas aún por su baja frecuencia son las metástasis adrenales, ováricas y gastrointestinales; en estos casos no se recomienda la resección, salvo en situaciones de paliación de síntomas.

Resección del tumor primario en enfermedad metastásica

Este es un escenario clínico donde las controversias son aún mayores, ya que la gran mayoría de los datos actualmente disponibles derivan de ensayos retrospectivos. Las conclusiones de algunos metaanálisis y otras publicaciones apuntan a un beneficio de SG de la resección del tumor primario en el cáncer de mama metastásico *de novo*. En estos estudios, las mujeres a las que se les ofreció la resección del tumor primario eran predominantemente más jóvenes, con mejor estado funcional y con menos carga metastásica, lo que introdujo el riesgo de sesgo de selección[100-105]. Otros estudios, no obstante, también retrospectivos, no han mostrado beneficio derivado de la resección del tumor primario en este contexto[106-108].

A la fecha se dispone de la información de cuatro estudios prospectivos aleatorizados, uno de ellos (Protocolo MF07-01) asignó aleatoriamente a los pacientes al momento de la presentación entre cirugía primaria *vs.* no cirugía, inicialmente no informó diferencias en la supervivencia a los tres años, sin embargo, con un seguimiento más prolongado de cinco años, la mediana de supervivencia mejoró significativamente para los pacientes que recibieron terapia local[108]. En el 2021 presentó una actualización del seguimiento a 10 años reportando una mediana de supervivencia de 46 meses para el grupo de cirugía *vs.* 35 meses para el grupo de terapia sistémica sola. Las controversias a este ensayo fueron un desequilibrio entre los brazos, ya que el grupo propuesto para la cirugía tenía pacientes más jóvenes, con mayor frecuencia ER positivos y *HER2* negativos, y con metástasis óseas únicas, factores que podrían haber tenido un impacto en el resultado. Los

otros tres estudios no han demostrado algún impacto en SG, del manejo local del tumor primario en cáncer de mama metastásico[109-112].

Además de estos cuatro estudios ya mencionados, en el año 2021 se publicó el estudio prospectivo BOMET MF1401, en el cual se segmenta la realización de la cirugía del tumor primario previo al manejo médico de elección en pacientes con enfermedad ósea oligometastásica, encontrándose en un seguimiento a tres años que el manejo locorregional prolonga la SG y disminuye la recurrencia locorregional[113,114].

Recientemente se publicó un estudio retrospectivo en el cual, mediante un análisis de partición recursiva, se agruparon los pacientes en tres grupos de acuerdo con sus factores pronóstico, adecuadamente balanceados. Se observó que todos los pacientes se beneficiaron de la cirugía, con una mediana de SG, cirugía *vs.* no cirugía de 72.7 *vs.* 42.9 meses, 47.3 *vs.* 30.4 meses, 23.8 *vs.* 14.4 meses (todos $p < 0.001$) en la subdivisión por grupos I, II y III, respectivamente[114]. Por lo tanto, parece ser una alternativa razonable que puede ser discutida con aquellas pacientes con características clínicas favorables como un buen estado general, menores de 55 años, enfermedad con RH positivos, *HER2* neu negativo, volumen tumoral limitado, predominantemente con metástasis óseas, sin metástasis cerebrales y en las que se considere poder obtener márgenes negativos independientemente del tipo de cirugía realizada que debe incluir forzosamente el control del primario y de la axila, debiéndose valorar el uso de radioterapia locorregional posterior a esta e incluso la reconstrucción mamaria, ya sea inmediata o diferida, individualizando el caso y discutiéndose todos estos puntos en un grupo multidisciplinario y con la paciente[115-119].

Wang et al. evaluaron en un estudio retrospectivo el beneficio añadido de la radioterapia en pacientes etapa IV *de novo* llevadas también a mastectomía en donde incluyeron a 1,458 analizadas, divididas en dos grupos adecuadamente balanceados, en donde el grupo con radioterapia añadida tuvo una mejoría en el pronóstico de sobrevida cáncer-específica y SG (*hazard ratio* [HR]: 0.739, intervalo de confianza del 95% [IC95%: 0.619-0.884, $p = 0.001$ y HR: 0.744, IC95%: 0.628-0.8810, $p = 0.001$, respectivamente)[120].

Resección paliativa del tumor primario en enfermedad metastásica

En este escenario clínico no hay controversia: la cirugía está indicada en pacientes con tumor fungante, ulcerado o hemorrágico, y tiene la finalidad de mejorar la calidad de vida, sin esperar impacto en supervivencia. En caso de tumores primarios no resecables, se puede considerar radioterapia paliativa[121].

Radioterapia en enfermedad metastásica

Su tratamiento distingue tres grupos, de acuerdo con diferentes características: a) pacientes con buenas condiciones generales, tumor primario controlado y enfermedad confinada a tres sitios o menos; b) mal estado funcional o diseminación metastásica extensa en quienes se requiere la paliación de síntomas como sangrado, infección, dolor o compresión, y c) los que requieren control local por sangrado, infección o dolor.

Radioterapia torácica en pacientes con enfermedad metastásica de novo

Se ha reportado mejoría en control local y supervivencia libre de progresión en pacientes que se someten a radioterapia con o sin cirugía, menores de 55 años, subtipos molecular RH positivo *HER2* negativo, RH positivo *HER2* positivo con metástasis óseas y hepáticas limitadas, tumores de bajo grado, buen estado funcional y respuesta parcial o completa al tratamiento sistémico[122,123].

Metástasis óseas en enfermedad polimetastásica

En metástasis asintomáticas de alto riesgo (> 2 cm, lesiones en cadera o articulación sacroilíaca, huesos largos con afección > 1/3 de la cortical, sitios de unión en columna C7-T1, T12-L1, L5-S1 o enfermedad vertebral con afección de elementos posteriores), la irradiación profiláctica con los esquemas convencionales ha demostrado mejorar la SG con disminución en los eventos esqueléticos en ensayos fase II[124]. Los esquemas que se utilizan son 30 Gy en 10 sesiones, 20 Gy en cinco sesiones e idealmente 8 Gy en dosis única. Puede considerarse reirradiación en caso de persistencia de los síntomas[125].

En metástasis óseas complicadas (compresión medular o síndrome de cauda equina) se prefiere la dosis única de 8-10 Gy en pacientes no candidatos a cirugía y esquemas más largos posterior a descompresión quirúrgica[126].

Metástasis cerebrales

En pacientes con metástasis cerebral única, primario controlado a nivel extracraneal y buen estado

funcional, las opciones de tratamiento incluyen: resección quirúrgica con radiocirugía a la cavidad, radiocirugía intracraneal dosis única 20-24 Gy en lesiones < 2 cm, 18 Gy para 2-3 cm o radioterapia estereotáctica hipofraccionada en lesiones > 3 cm en caso de que estas técnicas estén disponibles, o radioterapia a encéfalo total con o sin preservación de hipocampos y con o sin memantina[127,128].

En enfermedad cerebral limitada, la radiocirugía es una opción en caso de < 5 lesiones < 2 cm de diámetro con menos de 15 cc de volumen tumoral[129].

En caso de > 5 lesiones se utiliza la radioterapia a encéfalo total con o sin preservación hipocampal en dosis de 30 Gy en 10 fracciones, con o sin memantina[130].

Radioterapia estereotáctica corporal en enfermedad oligometastásica

Definida por 1-5 lesiones detectables por imagen[130]. En cáncer de mama, las metástasis óseas, pulmonares y hepáticas, son las más comunes[131].

Radioterapia estereotáctica corporal en metástasis óseas y vertebrales

Las indicaciones de radioterapia estereotáctica corporal (SBRT) en columna son: Karnofsky Performance Status (KPS) > 60, lesión única o múltiple (≤ 2 vértebras consecutivas o hasta tres sitios no contiguos), sin datos de compresión medular ni fractura patológica, tumor residual o recurrente posterior a cirugía y con un intervalo libre de enfermedad mayor de seis meses en casos de reirradiación[132].

En metástasis óseas no vertebrales la SBRT podría ser de utilidad en personas premenopáusicas con tumor primario controlado, adecuada respuesta a tratamiento sistémico, intervalo libre de enfermedad > 12 meses, metástasis dolorosas y subtipos moleculares de alto riesgo, no así en RH positivo y *HER2* negativo[89,133].

Radioterapia estereotáctica corporal en metástasis hepáticas

Indicada en pacientes no candidatas a manejo quirúrgico o que rechazan la cirugía. Los criterios para ofrecer esta técnica incluyen: adecuado funcionamiento hepático, ECOG (*Eastern Cooperative Oncology Group*) 0-2, enfermedad extrahepática ausente o estable, 1-5 lesiones con diámetro máximo de 10 cm en conjunto y volumen hepático sano > 700 cc. La quimioterapia debe suspenderse al menos tres semanas antes del procedimiento y debe reiniciarse dos semanas después de este[134,135].

Radioterapia estereotáctica corporal en metástasis pulmonares

Se indica en lesiones pequeñas con volumen < 11 cc y alcanzando una dosis biológica equivalente (BED) ≥ 100 Gy con una función respiratoria adecuada[136].

Radioterapia para control de síntomas

Se ofrece con esquemas hipofraccionados en casos de dolor, secreción fétida y enfermedad voluminosa, sangrado tumoral, urgencias oncológicas y carcinomatosis meníngea[137].

Evaluación y manejo de la recurrencia locorregional

La enfermedad recurrente exclusivamente en la mama o en la axila ipsilateral es un evento que se observa con una frecuencia menor al 10%, que puede suceder después de una cirugía conservadora o una mastectomía, ya sea en ambos casos con tratamiento axilar ipsilateral o sin él, seguidas o no de radioterapia total a la mama[138]. Inicialmente debe establecerse la extensión de la recurrencia, esto es si hay enfermedad a distancia o no. La distinción de enfermedad puramente recurrente o segundos primarios toma en cuenta factores clásicos como los de Warren, además de considerar cuadrante de la lesión, perfil de expresión hormonal, incluso genético, que puede verse modificado según el tratamiento previo[139].

Deben realizarse mamografía/ultrasonido y evaluación de la extensión (solo local, regional y/o a distancia). En caso de enfermedad a distancia, se procede a las recomendaciones de enfermedad metastásica. Los estudios para descartar enfermedad a distancia son la tomografía por emisión de positrones, la gammagrafía ósea o la tomografía computarizada.

El manejo de la enfermedad recurrente debe considerar que este evento en sí es un predictor de enfermedad a distancia y un factor pronóstico adverso, por lo que el tratamiento sistémico deberá considerarse en cualquiera de sus formas.

Manejo quirúrgico

Es imprescindible un abordaje multidisciplinario sobre el manejo de la recurrencia locorregional, acorde al tratamiento inicial del primario.

Las pacientes con mastectomía previa y con recurrencias en la pared torácica pueden ser llevadas a resección local. La mayoría se presentan en la piel y tejido subcutáneo, aunque las recurrencias a pared torácica pueden ocurrir en alrededor del 59% de los casos[140]. La resecabilidad dependerá de la extensión a la piel, posibilidad de cobertura de tejidos blandos y afectación de estructuras óseas. En las recurrencias locales aisladas que se consideren operables, es preferible el cierre primario simple o avance de colgados tras la resección amplia; cuando esto no es posible, se recomienda el uso de injertos de piel o transferencia de tejido autólogo debiendo considerar siempre que las reconstrucciones en un campo previamente radiado se asocian a una mayor tasa de complicaciones[141].

Por otra parte, en pacientes tratadas previamente con cirugía conservadora que presentan recurrencia local, aunque la mastectomía es aceptada como el manejo estándar en la recurrencia ipsilateral de cáncer de mama, en casos seleccionados, cuando las recurrencias son pequeñas y la relación mama: tumor lo permita, se puede considerar una segunda cirugía conservadora, siempre y cuando sea posible la aplicación de reirradiación. El estudio NRG Oncology/RTOG 1014, que incluyó pacientes con recurrencias locales de 3 cm o menores, sucedidas a un año o más después del tratamiento conservador inicial, confirmado como unicéntrico, con la evaluación mediante resonancia magnética preoperatoria, demostró que una segunda cirugía conservadora con reirradiación parcial a la mama permite conservación de esta con bajos índices de recurrencia locorregional (5.2% a 5 años). Las recurrencias localizadas en un cuadrante distinto o fuera del lecho quirúrgico inicial o con una histología diferente pueden representar un nuevo primario[142].

Las recurrencias axilares suelen afectar a los ganglios restantes y también pueden aparecer dentro de la grasa o el tejido conectivo de la axila. La determinación de la afección ganglionar previa y la extensión de la cirugía axilar previa es la clave del manejo posterior. Si se realizó disección axilar inicialmente, entonces la cirugía tendrá como objetivo la resección del tumor recurrente solamente; por el contrario, si se realizó biopsia de ganglio centinela (GC) o una linfadenectomía limitada (menor de 6 a 8 ganglios), entonces estará indicada una disección axilar completa, considerando que puede aumentar la probabilidad de linfedema, siendo la reestadificación axilar con disección de los niveles I y II el manejo estándar en este escenario. Sin embargo, la realización de GC posterior a cirugía axilar previa es posible, presentándose que la tasa de identificación varía del 66 al 71%[4] y la localización de GC no axilares aumenta hasta el 43%[142], aunque la tasa de GC positivo parece ser baja (8%). La tasa de falsos negativos es del 9.4% y la exactitud del procedimiento es del 97.1%. Se sugiere utilizar más de una técnica de identificación (colorante, radiotrazador, magnético, etc.) y considerar el posible drenaje extraaxilar. El mapeo linfático inverso se ha descrito como un medio alternativo para identificar y preservar los linfáticos y los ganglios que drenan del brazo en este tipo de pacientes[142].

Manejo con radioterapia

La decisión de ofrecer reirradiación en pacientes con recurrencia locorregional debe ser multidisciplinaria, tomando en cuenta la extensión de la enfermedad y manejo previo a la zona. En estos casos existe información que favorece la realización de una segunda cirugía conservadora con radioterapia parcial acelerada de mama como método de reirradiación[143].

Manejo sistémico

En mujeres con recurrencia local y después de que se haya realizado una resección completa de la enfermedad, la administración de tratamiento adyuvante ha mostrado una mejoría en supervivencia libre de enfermedad y global en todas las pacientes, con un mayor beneficio en el grupo de mujeres con RH negativos[144]. Al igual que en la recurrencia a distancia se recomienda, de ser posible, contar con una reevaluación del subtipo tumoral para determinar el mejor tratamiento sistémico recomendable, de acuerdo con el manejo previo, tiempo a la recurrencia y a las características de la paciente.

Seguimiento posterior al tratamiento con intención curativa y en enfermedad metastásica

Seguimiento posterior al tratamiento con intención curativa

Al concluir el tratamiento primario para el cáncer de mama, habitualmente con cirugía, quimioterapia y radioterapia, inicia la etapa de vigilancia y control denominada seguimiento. Los objetivos del seguimiento son: detectar recurrencias y cáncer de mama contralateral, evaluar y tratar complicaciones relacionadas con el tratamiento (p. ej., osteoporosis, segundos primarios), motivar a la paciente a continuar terapia endocrina y tratar sus efectos secundarios.

Tabla 2. Recomendaciones para el seguimiento

Procedimiento	Frecuencia
Instrucción a la paciente sobre los síntomas y signos de recurrencia	Al término de su tratamiento radical
Examen físico	Primeros 2 años cada 3 a 4 meses Tercero a quinto años cada 6 meses A partir del quinto año, anual
Autoexploración mamaria	Mensual
Mamografía	Anual
Marcadores tumorales	No se recomiendan
TC de tórax, abdomen, PET, centellografía ósea y enzimas hepáticas	Solo si hay sintomatología específica
Escrutinio de otros tumores (cervicouterino, colorrectal, ovárico, endometrial, etc.)	Seguir guías de detección temprana
Instrucciones a la paciente sobre ejercicio, actividad física y control de peso. Evaluar e impulsar la adherencia a la terapia endocrina y vigilar/tratar sus posibles eventos adversos. Hacer énfasis en el uso de métodos anticonceptivos (de barrera o definitivo)	En cada consulta

PET: tomografía por emisión de positrones; TC: tomografía computarizada.

Tabla 3. Seguimiento en pacientes con enfermedad metastásica

Evaluación	Basal	Quimioterapia	Terapia endocrina
Evaluación de síntomas	Sí	Antes de cada ciclo	Cada 1-3 meses
Examen físico	Sí	Antes de cada ciclo	Cada 1-3 meses
BH+PFH, QS	Sí	Cada 2-4 ciclos	Cada 2-6 meses
TC tórax-abdomen-	Sí	Cada 4 ciclos	Cada 4-6 meses
Pelvis	Opcional	Opcional	Opcional

BH: biometría hemática; PFH: pruebas de función hepática; QS: química sanguínea; TC: tomografía computarizada.

En la tabla 2 se describen las recomendaciones aceptadas internacionalmente para el seguimiento de estas pacientes. Es importante destacar que la aparición de metástasis luego del tratamiento primario adecuado es ajena al accionar médico; además, anticipar el diagnóstico de la recaída no aumenta la supervivencia ni la calidad de vida.

Seguimiento en pacientes con enfermedad metastásica

El objetivo es detectar progresión de la enfermedad, evitar toxicidad o el uso de un tratamiento ineficaz, así como la optimización de recursos. La reevaluación de la paciente está también indicada si hay deterioro, incremento de síntomas o aparición de nuevos signos, independientemente del intervalo transcurrido desde el control previo (Tabla 3).

Conclusiones

Se han hecho importantes avances en el manejo del cáncer de mama metastásico. Uno de los más trascendentes es el mejor conocimiento de la biología tumoral, lo que crea nuevos paradigmas de tratamientos específicos de acuerdo con cada subtipo biológico.

Es imperativo realizar biomarcadores en todas las pacientes, con el objetivo de tomar la mejor decisión terapéutica de forma individualizada. Si bien la piedra angular es la terapia sistémica, el manejo debe ser multidisciplinario, requisito indispensable para el tratamiento óptimo, que cuente con el apoyo de terapias locorregionales y tratamientos de soporte tempranos. El cáncer de mama metastásico es una enfermedad incurable; sin embargo, con las estrategias adecuadas se ha logrado incrementar la supervivencia libre de progresión y global con calidad de vida.

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Conflicto de intereses

Los autores declaran no tener conflicto de intereses.

Responsabilidades éticas

Protección de personas y animales. Los autores declaran que para esta investigación no se han realizado experimentos en seres humanos ni en animales.

Confidencialidad de los datos. Los autores declaran que en este artículo no aparecen datos de pacientes. Además, los autores han reconocido y seguido las recomendaciones según las guías SAGER dependiendo del tipo y naturaleza del estudio.

Derecho a la privacidad y consentimiento informado. Los autores declaran que en este artículo no aparecen datos de pacientes.

Uso de inteligencia artificial para generar textos. Los autores declaran que no han utilizado ningún tipo de inteligencia artificial generativa en la redacción de este manuscrito ni para la creación de figuras, gráficos, tablas o sus correspondientes pies o leyendas.

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