A systematic review and meta-analysis of bone metabolism in prostate adenocarcinoma

Ary Serpa Neto1, Marcos Tobias-Machado1,2, Marcos AP Esteves1,2, Marília D Senra2,3, Marcelo L Wroclawski1,2, Fernando LA Fonseca2,3, Rodolfo B dos Reis4, Antônio CL Pompeo1 and Auro Del Giglio*2,3

Background: Osteoporosis could be associated with the hormone therapy for metastatic prostate carcinoma (PCa) and with PCa per se. The objective of this review is to determine the incidence of bone loss and osteoporosis in patients with PCa who are or are not treated with hormone therapy (ADT).

Methods: The Medline, Embase, Cancerlit, and American Society of Clinical Oncology Abstract databases were searched for published studies on prostate cancer and bone metabolism. The outcomes assessed were: fracture, osteoporosis and osteopenia.

Results: Thirty-two articles (116,911 participants) were included in the meta-analysis. PCa patients under ADT had a higher risk of osteoporosis (RR, 1.30; p < 0.00001) and a higher risk of fractures (RR, 1.17; p < 0.00001) as compared to patients not under ADT. The total bone mineral density was lower in patients under ADT when compared with patients not under ADT (p = 0.031) but it was similar to bone mineral density found in healthy controls (p = 0.895). The time of androgen deprivation therapy correlated negatively with lumbar spine and total hip bone mineral density (Spearman’s rho = -0.490 and -0.773; p = 0.028 and 0.001, respectively) and with total hip t score (Spearman’s rho = -0.900; p = 0.037).

Conclusion: We found consistent evidence that the use of androgen deprivation therapy in patients with PCa reduces bone mineral density, increasing the risk of fractures in these patients.
significantly correlate with shorter survival in men with prostate cancer. When fracture history was evaluated, the median overall survival time was 39 months longer in men without a history of skeletal fracture. Therefore, a better understanding of the magnitude and prevalence of bone loss in these patients is critical [9,10].

The objective of this review is to determine the incidence of bone loss and osteoporosis in patients with PCa who are or are not treated with hormone therapy.

Methods
Search methods for identification of studies
Studies were identified through a computerized search of Medline (1966-2009), Cancerlit (1966-2009), and Embase (1990-2009), databases using the following as search query: "prostate cancer and [osteoporosis or bone mineral density]". A computerized search of the Proceedings of the Annual Meetings of the American Society of Clinical Oncology (ASCO) held between 1998 and 2008 was also performed to identify relevant studies published in abstract form. Lastly, all review articles and all cross-referenced studies from retrieved articles were screened for pertinent information.

Selection of studies
The meta-analysis was limited to studies that involved with the relationship of prostate cancer and/or hormone therapy with osteoporosis and in any language. For the incidence analysis all studies that report these rates were included (Table 1). Studies were excluded if fracture outcome or BMD data were not provided, or if they included patients with other bone or mineral disorders. When we found duplicate reports of the same study in preliminary abstracts and articles, we analyzed the data from the most complete data set.

Data extraction and statistical management
Data were independently extracted from each report by M.A.P.E, A.S.N and M.D.S, using a data recording form developed for this purpose. After extraction, data were reviewed and compared by A.S.N. Instances of disagreement between the two other data extractors were resolved by consensus among the investigators. Whenever needed, we obtained additional informations about a specific study by directly questioning the principal investigator.

For the fracture analysis, we computed a pooled estimate of the risk ratios (RRs) of each study using a fixed effect model according to Mantel and Haenszel and graphically represented these results in forest plot graphs. The homogeneity assumption was verified with a χ² test, using a df equal to the number of analyzed studies minus one. An estimate of the potential publication bias was performed by plotting the single study RR on a log-scale against the respective standard error (SE) creating a funnel plot. We used bivariate correlations with the Spearman’s rho coefficient to assess the relationship between ADT time and bone mineral density.

For all analyses, p values < 0.05 were considered significant. For publication bias, p values < 0.1 were considered significant.

Results
Literature search
The search strategy retrieved 361 unique citations: 314 from MEDLINE and 47 from EMBASE. Of these, 287 were excluded after the first screening, which was based on abstracts or titles, leaving 74 articles for full-text review (Figure 1). During this review, 42 articles were excluded for the following reasons: they involved randomized controlled trials with bisphosphonate therapy (n = 33); the same cohort was previously analyzed (n = 2); or the bone mineral density, t or z-scores or osteoporosis/osteopenia rate was not shown (n = 7). Finally, 32 articles (116,911 participants) were included in the meta-analysis.

Study characteristics
The characteristics of the 32 selected studies are shown in Table 1[11-41]. With two exceptions [14,41], all studies reported bone mineral density values as assessed by dual energy X-ray absorptiometry. Eleven studies reported biomarkers of bone turnover biomarkers, including alkaline phosphatase and cross-linked N-telopeptide of type I collagen (NTx). Twelve studies evaluated patients with prostate cancer (PCa) under androgen deprivation therapy (ADT); eight evaluated the same cohort of patients with PCa before and after the ADT; five evaluated patients with PCa, patients with PCa under ADT and healthy controls; three evaluated patients with PCa and patients with PCa under ADT; two evaluated patients with PCa under ADT and healthy controls; and two evaluated only patients with PCa.

The selected studies were published between 1997 and 2009, and the number of participants per study ranged from 12 to 50,613, for a total of 116,911 participants. At the baseline, the number of participants with PCa was 70,684, the number of participants with PCa under ADT was 45,161, and the number of healthy controls was 1,066. The mean age of the participants varied from 66 to 79 years (72.33 ± 3.12 years), and the mean time of ADT in the patients treated with this therapy varied from 2.9 to 120 months (36.98 ± 31.29 months). The risk ratios for osteoporosis, osteopenia and fractures were determined for seven, two and five studies respectively.

General characteristics of the patients
The general characteristics of the participants are described in Table 2. Patient age was similar in all groups. The total bone mineral density was lower in patients...
Table 1: Characteristics of studies included in the meta-analysis

| Source                          | Total No. Of Patients | DEXA | Biomarkers of Turnover | Type of Patients                  |
|--------------------------------|-----------------------|------|------------------------|-----------------------------------|
| Agarwall et al,[11] 2004       | 50                    | Yes  | None                   | PCa before and after ADT          |
| Ahlborg et al,[12] 2008        | 754                   | Yes  | None                   | PCa, PCa with ADT and controls    |
| Bernat et al,[13] 2005         | 18                    | Yes  | None                   | PCa with ADT                      |
| Berruti et al,[14] 2005        | 200                   | None | Yes                    | PCa with ADT                      |
| Bruder et al,[15] 2006         | 89                    | Yes  | Yes                    | PCa with ADT                      |
| Chen et al,[16] 2001           | 109                   | Yes  | None                   | PCa with ADT and controls         |
| Conde et al,[17] 2004          | 34                    | Yes  | None                   | PCa                               |
| Daniell et al,[18] 2000        | 54                    | Yes  | None                   | PCa, PCa with ADT and controls    |
| Diamond et al,[19] 2004        | 87                    | Yes  | Yes                    | PCa with ADT                      |
| Galvão et al,[20] 2008         | 72                    | Yes  | Yes                    | PCa before and after ADT          |
| Greenspan et al,[21] 2005      | 195                   | Yes  | Yes                    | PCa, PCa with ADT and controls    |
| Hatano et al,[22] 2000         | 218                   | Yes  | Yes                    | PCa with ADT                      |
| Higano et al,[23] 2004         | 17                    | Yes  | None                   | PCa before and after ADT          |
| Kiratli et al,[24] 2001        | 36                    | Yes  | None                   | PCa, PCa with ADT and controls    |
| Lee et al,[25] 2005            | 65                    | Yes  | None                   | PCa before and after ADT          |
| Maillefert et al,[26] 1999     | 12                    | Yes  | Yes                    | PCa before and after ADT          |
| Malcolm et al,[27] 2007        | 395                   | Yes  | None                   | PCa with ADT                      |
| Miyaji et al,[28] 2004         | 27                    | Yes  | Yes                    | PCa before and after ADT          |
| Morote et al,[29] 2007         | 390                   | Yes  | None                   | PCa before and after ADT          |
| Oefelein et al,[9] 2002        | 195                   | Yes  | None                   | PCa with ADT                      |
| Panju et al,[30] 2008          | 66                    | Yes  | None                   | PCa with ADT                      |
| Ryan et al,[31] 2007           | 120                   | Yes  | None                   | PCa with ADT                      |
| Shahinian et al,[32] 2005      | 50,613                 | Yes  | None                   | PCa and PCa with ADT              |
| Smith et al,[33] 2001          | 41                    | Yes  | Yes                    | PCa                               |
under ADT when compared with patients without ADT ($p = 0.031$), but it was similar to those found in healthy controls ($p = 0.895$). The total bone mineral density of the total hip was lower in patients under ADT when compared with patients without ADT ($p = 0.002$), but it was similar to those values found in healthy controls ($p = 0.211$). The $z$ score was similar in all groups, and the $t$ score of the lumbar spine and total hip was lower in patients under ADT when compared with patients with PCa without ADT ($p = 0.031$ and $p = 0.021$, respectively).

The time of androgen deprivation therapy correlated negatively with lumbar spine and total hip BMD (Spearman’s rho = -0.490 and -0.773; $p = 0.028$ and 0.001, respectively) and with total hip $t$ score (Spearman’s rho = -0.900; $p = 0.037$). (Figure 2)

The incidence of osteoporosis was higher in patients under ADT when compared with patients with PCa without ADT ($p < 0.001$), but it was lower when compared with the healthy controls ($p < 0.001$). However, patients under ADT had a higher number of fractures when compared with patients with PCa and healthy controls ($p < 0.001$ for both comparisons).

**Risk of osteoporosis and fracture**

Among the five selected studies that analyzed patients under ADT and patients with PCa only, all found an association between androgen deprivation therapy and an increased risk of osteoporosis. Patients with PCa under androgen deprivation therapy had an increased risk of developing osteoporosis as compared to patients with PCa who were not under ADT, with a pooled risk ratio (RR) of 1.30 (95% CI, 1.22 - 1.40) (Figure 3A).

Of the two studies that analyzed patients with PCa not under ADT and healthy controls, neither found an association between PCa and an increased risk of osteoporosis. Patients with PCa without ADT had a reduced risk of developing osteoporosis as compared to healthy controls, with a pooled RR of 0.39 (95% CI, 0.16 - 0.96) (Figure 3B). Patients under ADT had a higher risk of developing osteoporosis when compared to healthy controls (RR, 2.26; 95% CI, 1.00 - 5.09).

Among the five selected studies that analyzed patients with PCa under ADT and patients with PCa without ADT, all found an association between androgen deprivation therapy and an increased risk of fractures, with a pooled RR of 1.17 (95% CI, 1.14 - 1.20), but with significant heterogeneity of RRs across studies ($p < 0.0001$; $I^2$, 2006

| Study | Participants | ADT | PCa | PCa and PCa with ADT |
|-------|--------------|-----|-----|----------------------|
| Smith et al.[34] 2005 | 11,661 | Yes | None | PCa and PCa with ADT |
| Smith et al.[35] 2006 | 12,120 | Yes | None | PCa and PCa with ADT |
| Spanjol et al.[36] 2008 | 398 | Yes | None | PCa with ADT |
| Stoch et al.[37] 2001 | 257 | Yes | Yes | PCa, PCa with ADT and controls |
| Townsend et al.[38] 1997 | 224 | Yes | None | PCa with ADT |
| Wei et al.[39] 1999 | 32 | Yes | None | PCa before and after ADT |
| Yamada et al.[40] 2007 | 204 | Yes | Yes | PCa with ADT and controls |
| Alibhai et al.[41] 2009 | 38,158 | None | None | PCa with ADT and controls |

**DEXA:** Dual energy X-ray absorptiometry; **PCa:** Prostate cancer; **ADT:** Androgen deprivation therapy

![Flowchart of the meta-analysis](image-url)
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96%). These measurements of heterogeneity were likely a result of the extremely large overall number of participants in our analysis (111,573 participants). The point estimates of the RRs were consistently greater than one in all studies. (Figure 4)

To explore the study heterogeneity, we performed stratified analyses across a number of key study characteristics and clinical factors (Table 3). The finding that patients under ADT had an increased fracture risk was consistently found in all of the stratified analyses. For example, when stratified by the type of the fracture, patients under ADT seemed to have a higher risk of lumbar spine fracture than of hip/femur fracture.

Publication bias

The visual inspection of the Begg funnel plot that is related to figure 3A did not reveal asymmetry (p = 0.219) (Figure 5A). This finding is consistent with a small possibility of publication bias, as confirmed by the Begg test (z = 1.47; p = 0.142). The visual inspection of the Begg funnel plot that is related to figure 3B did not reveal asymmetry (p = 0.193) (Figure 5B). This results excludes the possibility of publication bias, as confirmed by the Begg test (z = 0.68; p = 0.497).

Discussion

An extensive body of literature reports on the association between androgen deprivation therapy and the incidence of osteoporosis. All the five studies that we identified, and that met the inclusion criteria, indicated a positive association between ADT and osteoporosis. In relation to fractures, all four of the identified studies indicated a positive association between ADT and the incidence of fractures. Furthermore, the association persisted and remained statistically significant across a number of stratified analyses that explored clinical and study quality factors.

Observational primary studies usually cannot prove causality. However, the studies in this review presented an appropriate temporal relationship; the androgen deprivation therapy and the diagnosis of prostate cancer diagnosis preceded the incidence of osteoporosis and fractures in all of the studies. Furthermore, androgen deprivation therapy depletes the circulating levels of oestrogens and androgens that maintain bone mass

| Table 2: General characteristics of the participants |
|-----------------------------------------------|
| PCa and ADT (n = 26,082) | P* | PCa w/ADT (n = 51,605) | P** | Controls (n = 1,066) | P*** |
|------------------------------|-----|-------------------|-----|-------------------|-----|
| Age (years) | 72.3 ± 3.12 | > 0.05 | 70.2 ± 2.81 | > 0.05 | 70.3 ± 3.30 | > 0.05 |
| ADT time (months) | 36.9 ± 31.2 | --- | --- | --- | --- | --- |
| Total BMD (g/cm²) | 0.90 ± 0.34 | 0.031 | 1.07 ± 0.11 | 0.760 | 0.96 ± 0.20 | 0.895 |
| LS BMD (g/cm²) | 1.02 ± 0.10 | 0.083 | 1.10 ± 0.13 | 0.806 | 1.05 ± 0.18 | 0.868 |
| TH BMD (g/cm²) | 0.89 ± 0.08 | 0.002 | 1.010.08 | 0.823 | 0.97 ± 0.03 | 0.211 |
| t score (Total) | -1.30 ± 1.10 | 0.282 | -0.26 ± 1.14 | --- | --- | --- |
| t score (LS) | -0.27 ± 1.21 | 0.031 | 0.25 ± 0.07 | --- | --- | --- |
| t score (TH) | -0.94 ± 0.24 | 0.021 | -0.55 ± 0.07 | --- | --- | --- |
| z score (Total) | -0.30 ± 0.69 | 0.164 | 0.54 ± 0.15 | --- | --- | --- |
| z score (LS) | -0.27 ± 1.31 | --- | --- | --- | --- | --- |
| z score (TH) | -0.33 ± 0.65 | 0.555 | 0.05 ± 0.35 | --- | --- | --- |
| Osteoporosis (%) | 5.30 | < 0.001 | 2.89 | < 0.001 | 10.3 | < 0.001 |
| Osteopenia (%) | 1.01 | < 0.001 | 0.15 | < 0.001 | 1.4 | 0.278 |
| Fracture (%) | 17.56 | < 0.001 | 15.62 | < 0.001 | 1.5 | < 0.001 |
| Vertebral fracture (%) | 2.96 | < 0.001 | 1.90 | --- | --- | --- |
| Superior member fracture (%) | 4.45 | < 0.001 | 2.47 | --- | --- | --- |
| Inferior member fracture (%) | 9.77 | < 0.001 | 7.38 | --- | --- | --- |

LS: Lumbar spine; TH: Total hip
*: PCa and ADT vs PCa w/ADT
**: PCa w/ADT vs Controls
***: Controls vs PCa and ADT
through suppression of bone reabsorption and promotion of bone formation [6]. These facts impart biological plausibility to our findings on the association between PCa and ADT with osteoporosis and fractures as shown by the forests plots (Figure 3A, 3B and 4).

The lack of adjustment for the presence of metastasis (only one study adjusted for this factor), calcium ingestion (no studies) and genetic predisposition (no studies) must be considered as a limitation of our study. The presence of metastasis, a low calcium ingestion and patients with history of osteoporosis in the family had a higher risk of osteopenia, osteoporosis and fractures.

It is estimated that two million men are affected by osteoporosis in the United States. Although men experi-

![Figure 2 Scatter plot of lumbar spine (black circles) and total hip (white circles) BMD and ADT time](image)

**Figure 2** Scatter plot of lumbar spine (black circles) and total hip (white circles) BMD and ADT time.

![Figure 3 Adjusted risk ratios](image)

**Figure 3** Adjusted risk ratios. A, Adjusted risk ratio of osteoporosis for patients under ADT as compared to patients not under ADT. B, Adjusted risk ratio of osteoporosis for patients with PCa as compared to healthy controls.
ence a gradual age-related loss of BMD of 7 to 12% per
decade beginning at age 30, primary male osteoporosis is
not common [42]. Most men who have clinically signif-
cant osteoporosis are older than 70 years of age and have
risk factors that contribute to decreased bone mineraliza-
tion, such as hypogonadism, thyroid and parathyroid dis-
orders, glucocorticoid excess, alcoholism, osteomalacia,
and malignancy [43]. The relationship between decreased
BMD and ADT is well established. Androgen suppression
reduces BMD approximately 3% to 7% per year [44].
Recent reports have demonstrated that men who have
prostate cancer and are receiving ADT have BMD mea-
surements from 6.5% to 17.3% lower than men who are
not treated with ADT [7]. One study reported that spinal
and femoral BMD values were 1.7% and 5.2% less after
two years and 14% and 28% less after 10 years of ADT,
respectively, as compared to age-matched control sub-
jects [24].
Although some studies defend the idea that PCA
patients (without ADT) have lower levels of BMD and
higher rates of osteoporosis, we were not able to verify
this finding in our study. In fact, patients with prostate
cancer showed similar levels of BMD and lower rates of
osteoporosis when compared with healthy controls.
Assessed individually, three studies showed similar levels
of BMD between PCA patients and healthy controls
[21,24,37], one showed higher levels for the PCA group
[12] and one showed lower levels [18]. With respect to
osteoporosis, all studies showed lower rates in the PCA
group as compared to healthy controls [12,21]. One
potential explanation for these findings is the highly
debated association of a high endogenous androgen levels
with the risk of prostate cancer, which may potentially
explain the higher BMD seen in patients with PCA before
they receive ADT as compared to normal men [45]. We
were unable to evaluate this hypothesis in our study
because only two of the evaluated studies had data on tes-
tosterone levels. Nevertheless, the prevalence of osteopo-
rosis in man with PCA cannot be neglected.

Wei et al [39] found that 63% of patients who had hor-
mone-naive prostate cancer had osteopenia or osteopo-
rosis. In a larger study, Smith et al [33] demonstrated that
34% prostate cancer patients without exposure to ADT
had dual-energy x-ray absorptiometry (DEXA) criteria

**Table 3: Stratified analyses of pooled relative risk of fractures for patients under androgen deprivation therapy**

| Stratified Analysis                   | Patients | Pooled RR (95% CI) | Heterogeneity |
|--------------------------------------|----------|--------------------|---------------|
| Incidence of fractures as the primary outcome |          |                    |               |
| Yes                                  | 111,573  | 1.17 (1.14 - 1.20) | 0.0001        |
| No                                   | ---      | ---                | ---           |
| Type of outcome measure              |          |                    |               |
| Self-reported                        | 50,613   | 1.06 (1.02 - 1.10) | Not applicable|
| Ambulatory                           | 22,802   | 1.18 (1.12 - 1.24) | 0.02          |
| Bone metastases in the sample        |          |                    |               |
| Yes                                  | 50,678   | 1.06 (1.02 - 1.10) | 1.18          |
| No                                   | 22,737   | (1.12 - 1.23)      | 0.01          |
| Mean follow-up, y                    |          |                    |               |
| ≥ 5                                  | 61,295   | 1.08 (1.04 - 1.11) | 0.04          |
| < 5                                  | 12,120   | 1.29 (1.18 - 1.43) | Not applicable|
| Type of fracture                     |          |                    |               |
| Lumbar spine fracture                | 74,394   | 1.33 (1.22 - 1.45) | 0.93          |
| Inferior member fracture             | 74,394   | 1.15 (1.10 - 1.20) | 0.001         |
for osteopenia or osteoporosis. Conde et al [17] reported a high prevalence of osteopenia (73.5%) and osteoporosis (17.6%) in 34 men who had non metastatic, hormone-naive prostate cancer. We could see that prostate cancer and ADT are strongly associated with bone metabolism modifications and, in these studies, advanced age, lower body mass index, and elevated prostate specific antigen levels correlated significantly with decreased BMD.

Fractures are associated with substantial morbidity and mortality. Men who experience hip fractures suffer greater impairment and have a higher rate of fracture-related mortality than women [46]. Approximately 20% to 30% of hip fractures occur in men, and 50% to 60% of men die within one year of the fracture [47]. The detrimental association between fracture and mortality extends to men who have prostate cancer. Oefelein and colleagues identified a negative association between skeletal fracture and overall survival in 195 prostate cancer patients treated with chronic ADT [9].

The bone mass of a normal adult is the outcome of a dynamic equilibrium between bone formation and bone resorption. The latter step is regulated by a family of proteins that include receptor activator of nuclear factor k-B (RANK), RANK ligand (RANKL) and osteoprotegerin (OPG). Binding of RANKL to RANK on the surfaces of osteoclast precursors will trigger maturation, activation, and prolonged survival of these cells. Thus, RANKL promotes bone resorption. Vitamin D, parathyroid hormone, tumour necrosis factor-α (TNF-α), activated T-cells, and glucocorticoid therapy all increase this ratio, promoting bone resorption. Estrogen deficiency states produce osteoporosis because normal levels of 17β-estradiol inhibit RANKL production and stimulate OPG. Testosterone stimulates osteoblasts, inhibits the apoptosis of both osteoblasts and osteoclasts, and is a precursor of estrogen via aromatization; its net effect is to stimulate bone formation. In males under ADT, both testosterone and estrogen levels fall, shifting the balance of bone turnover toward resorption [48]. ADT does not have a significant impact on serum calcium, 25-hydroxyvitamin D, or PTH, but epidemiological studies have suggested that high levels of calcium intake may suppress PTH and ultimately 1,25-dihydroxyvitamin D and associated with increased risk of prostate cancer [49].

Current American Society of Clinical Oncology (ASCO) guidelines and expert panels suggest that patients under ADT with clinically significant bone loss should receive bisphosphonates, regardless of hormonal and metastatic status, and preclinical and clinical data show that bisphosphonates can also prevent and treat CTILB and may inhibit malignant bone disease development in patients with early stage disease [7,10].

Conclusions
We conclude that patients with prostate cancer under androgen deprivation therapy had lower levels of BMD and higher rates of osteoporosis and fractures than patients with PCa not under ADT and healthy controls. Prostate cancer per se does not seem to be a risk factor for osteoporosis. However, the incidence of fractures was higher than that found in healthy controls, indicating that these patients may have had an additional, albeit unknown, mechanisms that could explain these findings. Although several studies in the literature have shown similar results, our study analyzed a larger number of studies and patients, providing consistent evidence on PCa, androgen deprivation therapy, osteoporosis and fracture risk.

Competing interests
The authors declare that they have no competing interests.
Authors' contributions
ASN - Conceived the study and participated in the design of the study, data collection, data extraction, statistical analysis and drafted the manuscript. Read and approved the manuscript. MTM - Conceived the study and participated in the design of the study and coordination. Read and approved the manuscript. MAPE - Conceived the study and participated in the design of the study and coordination. Read and approved the manuscript. FLAF - Conceived the study and participated in the design of the study, data collection and coordination. Read and approved the manuscript. ACLP - Participated in the design of the study and coordination. Read and approved the manuscript. ADG - Conceived the study and participated in the design of the study and coordination. Read and approved the manuscript. MLW - Conceived the study and participated in the design of the study and coordination. Read and approved the manuscript. MDS - Participated in the data collection and drafted the manuscript. Read and approved the manuscript. ASN - Conceived the study and participated in the design of the study, data collection, data extraction, statistical analysis and drafted the manuscript. Read and approved the manuscript. HIAE; São Paulo, Brazil, 3Oncology Division; Dept. of Clinical Oncology and Haematology; ABC Medical School (FMABCS); Santo André, Brazil; 4Research Institute; Albert Einstein Jewish Hospital (IEPEHIAE); São Paulo, Brazil; 5Oncology Division; Dept. of Clinical Oncology and Haematology; ABC Medical School (FMABCS); Santo André, Brazil; 6Research Institute; Albert Einstein Jewish Hospital (IEPEHIAE); São Paulo, Brazil.

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