Appropriate Chemotherapy Dosing for Obese Adult Patients with Cancer:
American Society of Clinical Oncology Clinical Practice Guideline

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## Data Supplement 1 - Evidence Table

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<th>Author, Year</th>
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<tr>
<td>Lyman, 2003</td>
<td>To assess practice patterns in adjuvant chemotherapy for ESBC and to define the incidence and predictive factors of RDI</td>
<td>Review</td>
<td>Chemotherapy AC, DMF, CAE</td>
<td>BMI as a measure of obesity was associated with increasing reductions in RDI. The association between BMI based on WHO criteria and RDI was related to a reduction in planned dose-intensity. Dose reductions ≥ 15% occurred in 36.5% of patients, and there were treatment delays ≥7 days in 24.9% of patients, resulting in 55.5% of patients receiving RDI less than 85%. Nearly two thirds of patients received RDI less than 85% when adjusted for differences in regimen dose-intensity.</td>
<td>Patients with high BMI or BSA of ≥ 2 m2 or greater also experienced greater reductions in dose-intensity. The association between BMI based on WHO criteria and RDI was related to a reduction in planned dose-intensity. Dose reductions ≥ 15% occurred in 36.5% of patients, and there were treatment delays ≥7 days in 24.9% of patients, resulting in 55.5% of patients receiving RDI less than 85%. Nearly two thirds of patients received RDI less than 85% when adjusted for differences in regimen dose-intensity.</td>
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<tr>
<td>Lyman, 2004</td>
<td>To survey practice patterns nationwide treating patients with NHL and establish RDI and incidence of FN and CSF use</td>
<td>Review</td>
<td>Chemotherapy CHOP, CHOP-R, CNOP</td>
<td>MVA for FN - BSA &gt; 2 m2 AOR (95% CI): 0.71 (0.57-1.14) No data on overweight or obese RDI</td>
<td>Risk of FN in patients w/ BSA &gt; 2 m2 (22.6%) No data on overweight or obese RDI</td>
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Midlbehr, 2007
To evaluate the association between BMI and outcomes in women with advanced or recurrent endometrial cancer treated with doxorubicin/cisplatin. A secondary objective was to report the proportion of women whose chemotherapy dosing was capped (<95%) and to determine if that was associated with outcomes.

Methods
Chemotherapy: cisplatin doxorubicin (Adriamycin)
Total N=949
(N=131 from GOG107, N=123 from GOG122, N=169 = N=171 from GOG139, N=157 from GOG163, N=128 from GOG177); 945 in analyses (6 excluded due to missing height or weight data)
Endometrioid 470/949 (50.1%); BM; 50.1%+ 6.1; Clear cell 284/949 (30.0%); BM: 27.1+ 6.1; Serous 286/949 (30.1%); BM: 29.1+ 6.5; Other 256/949 (27.0%); BMI 29.1+ 7.1; p=0.04; tumor grade p=0.04
stage I 189/949 (19.9%); stage II 227/949 (23.9%); Recurrent 353/949 (36.6%); p=0.04

Efficacy
There was no significant difference in OS across BMI groups for either stage III (P=0.02) or stage IV (P=0.87) or recurrent patients (P=0.77); but after adjusting for age, status, stage, histologic type, grade and protocol, there was significant evidence that BMI was associated with OS P=0.02 among patients with primary stage III or IV disease. The morbidly obese patients were at increased risk of death compared to the normal weight patients (HR 1.86, 95% CI 1.62-2.19). The association between BMI and OS was not evident for recurrent patients (P=0.36). No significant difference between BMI and DFS or treatment response (P=0.92) in either group.

Of 117 patients with BSA > 2.5, dosing was capped in 43% for doxorubicin, 44.4% for cisplatin, and 46.2% for either one. Compared with patients with uncapped dosing, capped dosing was not statistically significantly associated with a worse prognosis (HR 1.05; CI 0.92 to 1.19; P=0.33); adjusted for age, pre-treatment performance status, disease stage, histologic type, tumor grade, and protocol).

Conclusions
BMI was not predictive of DFS, although morbidly obese patients had decreased OS in primary stage III/IV patients. Toxicities decreased with increasing BMI, perhaps secondary to capped dosing.

Lindman, 2007
To investigate (Phase II Study) a tailored and dose-escalated regimen that is active and feasible in metastatic breast cancer and to provide a pragmatic way of overcoming shortcomings of BSA-based dosing.

Methods
Chemotherapy: 5 FU with or w/o leucovorin (F) Epirubicin (E) Cyclophosphamide (C)
N= 26 patients
The given average dose intensity was F 185 mg/m2/2, E 26.4 mg/m2/2 and C 336 mg/m2/2 (representing 93%, 132% and 168% of intended doses of standard regimen).

Efficacy
Overall response rate for 21 patients was 81% (CI 69% to 91%); including six complete responders (23%; CI 7%–36%). For the 13 patients receiving the the highest dose intensity, 11 responded compared with 10 patients among the 13 patients with the lowest dose intensity.No significant correlation was observed between Epirubicin and Cyclophosphamide intensity and OS or TTP. Median TTP 14 months; median OS 36 months, with a median f/up of 113 months.
Delivered dose intensity was high but varied substantially between patients (ranges F 126-202, E 14.6-38.8, C 160-510 mg/m2/w).

Conclusions
Delivery of standard doses of chemotherapy based on patients’ BSA will result in marked inter-individual variations in toxicity, which may be explained by the large differences in drug clearance and sensitivity between patients. Retrospective studies in early breast cancer have indicated that lack of toxicity could be a sign of undertreatment which could compromise survival.

Abith, Brently, 2003
To evaluate the chemotherapy-induced toxicity in obese cancer patients with dosing based on ABW.

Methods
Chemotherapy: cyclophosphamide, methotrexate, 5 FU 225, cyclophosphamide, doxorubicin, 5FU 12.5%, Other doxorubicin regimens 10%; 5 FU with leucovorin 14%; Cyclophosphamide regimens 17%; Carboplatin regimens 9%; other 18%
N=179/502 (29%) patients were obese (BMI ≥ 27.3 kg/m2 for females and 27.8 kg/m2 for males)
Arm A: N=147/178 obese cancer patients 24% received full doses and were evaluable

Toxicities
Dose-limiting (e.g. neutropenia, fever, severe thrombocytopenia associated with significant bleeding and/or requiring platelet transfusion) was noted in 16/467 patients (11% in first cycle, 7% in second cycle and 4% in third cycle). The incidence of Grade III-IV nonhematologic toxicity (e.g. alopecia, nausea, vomiting) were not dose limiting in obese patients.

Conclusions
The conclusion was that calculation of standard chemotherapy dose according to ABW in obese patients is relatively safe.
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<td>Madarnas, 2001</td>
<td>To determine the distribution of body size and prevalence of obesity in the breast cancer population and to determine clinician chemotherapy dosing patterns.</td>
<td>Retrospective &lt;br&gt; Chemotherapy: 5-FU with or w/o leucovorin (F), cyclophosphamide (C), methotrexate (M). &lt;br&gt; N=10,128 &lt;br&gt; Initial population was 3,048 patients with invasive breast cancer who had received systemic therapy (neoadjuvant, adjuvant, or palliative); 63% = 1922/3048 were evaluable (mean BMI 26.4 ± 5.3 kg/m², 54% were overweight, 2% severely obese, 18% moderately obese. Mean BSA was 1.7 ± 0.2 m² and only 5% had a BSA ≥2 m². &lt;br&gt; Subgroup treated for curative intent N=532; 27 ± 5.4 kg/m²; 58% were overweight, 2% severely obese; 23% were moderately obese. Mean BSA 1.7 ± 0.2 m² and 8% had BSA ≥2 m².</td>
<td>% of group with 2 or 3 drug reductions - Overall 373/532 70%, &lt;1.5 BSA 26.44 (59%) had reduction, BSA 1.5-1.9 31/449 had 69% reduction, and ≥2 BSA 36.59 had 59% reduction. Results of subgroup: 7% received a level I/II* reduction at the start of their adjuvant chemo. While the majority of women in both BSA categories received ≥ 85% of ideal dose at cycle 1. The mean reduction in dose at cycle one was significantly higher in the high ≥2m2 BSA group (5.8 ± 11.3% vs 0.8 ± 11.7% for &lt;2m group, P=0.02. AND 4.3 ± 6.2% versus 6.7 ± 13.1% in the BMI ≥25 and ≥2, respectively P=0.008. Only 34% of chemotherapy reductions of ≥15% were in the BSA ≥2m2, 76% were in the BMI ≥2.5 kg/m² group.</td>
<td>No statistically significant difference in PFS or OS across 3 groups.</td>
<td>Overall 373/532 70%, &lt;1.5 BSA 26.44 (59%) has reduction, BSA 1.5-1.9 31/449 had 69% reduction, and ≥2 BSA 36.59 had 59% reduction. No differences in dosing patterns of epirubicin or doxorubicin were noted on the basis of BSA above or below 2m2, nor on the basis of BMI above or below 25 kg/m². Significantly greater reductions in the dose of methotrexate among women deemed large on the basis of BSA and BMI. Methods for reducing doses were rarely stated in records. When identified the rationale was a desire to &quot;scale back&quot; the dose for a large individual.</td>
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<td>Wright, 2008</td>
<td>This study assessed the association between BMI and outcome for ovarian cancer patients treated with carboplatin-based chemotherapy based on Jelliffe formula, so obese women often receive subtherapeutic dose.</td>
<td>Retrospective &lt;br&gt; Chemotherapy: carboplatin: AUC 7.5; paclitaxel (Taxol): 175 mg/m². &lt;br&gt; N=387/392 ovarian cancer patients &lt;br&gt; Arm A (N=194) : BMI&lt;25.0 &lt;br&gt; Arm B (N=122) : BMI 25.0-29.9 &lt;br&gt; Arm C (N=71) : BMI=30.0</td>
<td>No statistically significant difference in PFS or OS across 3 groups. “Trend” toward increased risk for disease progression in obese patients.</td>
<td>Significantly less thrombocytopenia, dose delays, and dose modifications in obese women.</td>
<td>Obese ovarian cancer patients treated with carboplatin experience substantially less toxicity than normal weight women. The lower toxicity suggests that obese patient may be receiving a substandard dose. RR: 1.25, 95% CI: 0.93-1.69, P=0.14 in obese patient compared to normal after adjustment for age, PS, histology, and residual disease.</td>
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Meyerhardt, 2003

To study the influence of BMI on recurrence, OS, and toxicity in a large adjuvant chemotherapy trial of patients with high-risk, stage II and stage III colon cancer studied.

Methods

- Retrospective
- Chemotherapy: 5-FU with or w/o leucovorin; LDLV: low-dose leucovorin; HLDLV: high-dose leucovorin; LEV: leucovorin; 5-FU: 5-fluorouracil
- Immunotherapy: adjuvants (BCG)

Efficacy

- The administration of 95% of the expected first 5-FU dose was not predictive of overall mortality or disease recurrence in the multivariate model. There were no differences between men and women with regard to the completion of therapy (78.1% men vs. 76.3% women; P=0.10) and underdosing of chemotherapy (3.6% men vs. 2.6% women); similar results were observed when this comparison was restricted to obese patients

Toxicities

- Obese patients had significantly lower rates of Grade 3-4 leukopenia and lower rates of any Grade 3 toxicity compared with patients of normal weight

Conclusions

- Among women with Stage II-III colon carcinoma, obesity was associated with a significant increase in overall mortality as well as a borderline significant increase in disease recurrence. Nonetheless, obesity was not associated with any increase in chemotherapy-related toxicity. The authors hypothesized that this gender interaction may be related to the effects of estrogen.

Despite protocol specifications to dose patients based on their actual weight, there were modest differences in the percentages of women who were underdosed (2.0% of women with BMI 21.0 kg/m2, 2.1% of women with BMI 21.0–24.9 kg/m2, 1.6% of women with BMI 25.0–27.4 kg/m2, 2.9% of women with BMI 27.5–29.9 kg/m2, and 4.9% of women with BMI 30.0 kg/m2; P = 0.18).

Meyerhardt, 2004

To study the relationship between body mass index (BMI) and rates of sphincter-preserving operations, overall survival, cancer recurrence, and treatment-related toxicities in patients with rectal cancer.

Methods

- Retrospective
- Chemotherapy: 5-FU with or w/o leucovorin
- Immunotherapy: adjuvants

Efficacy

- obese men with rectal cancer were also more likely than normal-weight men to have a local recurrence (hazard ratio [HR], 1.61; 95% CI, 1.00 to 2.59). In contrast, obesity was not predictive of cancer recurrence in women, nor was BMI predictive of overall mortality in either men or women. Underweight patients had an increased risk of death (HR, 1.45; 95% CI, 1.08 to 1.95) compared with normal-weight patients but no increase in cancer recurrences. Given the small percentage of patients receiving less than 95% of the expected first 5-FU dose, there was not sufficient statistical power to stratify patients by underdosing or not

- Among patients who were normal-weight or heavier, there were no appreciable differences in the rates of chemotherapy underdosing (0.1% of patients with BMI 20 kg/m2, 2.0% of patients with BMI of 21 to 24.9 kg/m2, 1.9% of patients with BMI of 25 to 26.9 kg/m2, 2.0% of patients with BMI of 27 to 29.9 kg/m2, and 2.3% of patients with BMI of 30 kg/m2; P = .66)

Toxicities

- Among all study participants, obese patients had a significantly lower rate of grade 3 to 4 leukopenia, neutropenia, and stomatitis and a lower rate of any grade 3 or worse toxicity when compared with normal-weight individuals

Conclusions

- Increasing BMI in male patients with rectal cancer is associated with a decreased likelihood of sphincter preservation and a higher chance of local recurrence. For both men and women, underweight and obese patients experience less toxicity associated with adjuvant chemotherapy, suggesting that ABW of fluorouracil for obese patients is justified.

Not statistically powered to determine effect of other under dosing on outcomes.
To analyze the relationship between BMI and OS was assessed in patients with ovarian cancer.

### Methods

**Retrospective**

Chemotherapy: carboplatin: all patients N=1067
doxorubicin (Adriamycin): DC N=516
paclitaxel (Taxol): Arm A 25.9 BMI, N=129/1075
Arm B: >30 BMI, N=129/1075, /% of patients PC=36%
Arm C: 25-29.9 BMI, N=129/1075, /% of patients DC=49%
Arm D: >30 BMI, N=129/1075, /% of patients DC=49%

Result Arm A: Median OS was 32.9 months (95% CI 23.3-42,4, n = 193). Median PFS was 14.7 months (95% confidence interval) CI 11.6-17.8, n = 59
Result Arm B: Median OS was median not attained in the ideal weight group (n= 374). Median PFS was 14.7 months (95% CI 13.3-16.1, n = 374)
Result Arm C: Median OS was 33.1 months (95% CI 25-44.7, n = 103). Median OS was Median PFS was 47.4 months (95% CI 32.6-61.8, n = 303)
Result Arm D: Median OS was 34.3 months (95% CI 26.9-41.7, n = 129). Median PFS was 16.6 months (95% CI 11.8-21.4, n = 129)

**Toxicities**

No data

Obese patients with epithelial ovarian cancer do not have a poorer prognosis, provided that they receive optimal doses of chemotherapy based on measured GFR and actual body weight.

### Conclusions

**Obese women with breast cancer often receive intentionally reduced doses of adjuvant chemotherapy. Administration of initial and overall full weight-based doses of adjuvant chemotherapy in overweight and obese women is likely to improve outcomes in this group of patients.**
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<tr>
<td>Geogiadis, 1995</td>
<td>To evaluate the clinical course of cohorts of patients treated for SCLC to determine if obese patients had an increase in toxicity</td>
<td>Retrospective</td>
<td>Chemotherapy: cisplatin - after 1986 N=54 with etoposide plus 2 x daily chest radiotherapy cyclophosphamide - before 1986 N=47, with or without radiotherapy etoposide (VP-16) - after 1986 N=54 with cisplatin chest radiotherapy</td>
<td>N=262 evaluable patients [146/262 (56%) had limited stage SCLC and 11/262 (44%) had extensive disease]</td>
<td>Efficacy:</td>
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<td>Arm A: Normal BMI</td>
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<td>Arm B: Obese BMI</td>
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<td>Arm C: Severely obese</td>
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<td>22.1% were obese, 10.7% were severely obese. The percentage of the intended dose of chemotherapy actually given was more than 99% for both cycles of chemotherapy within all cohorts.</td>
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<td>Rosner, 1996</td>
<td>To examine the data from a large clinical trial to determine if chemotherapy dosing according to actual body weight places obese stage 2 breast patients at greater risk of toxicity.</td>
<td>Retrospective</td>
<td>Chemotherapy: cyclophosphamide (C) doxorubicin (A) 5-fluorouracil (F)</td>
<td>N=1,471/1,572 evaluable</td>
<td>Toxicities:</td>
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<td>3 levels of dose intensity</td>
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<td>Arm A: CAF 600/60/600; # of obese patients n = 194</td>
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<td>Arm B: CAF 400/40/400; # of obese patients n = 208</td>
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<td>Arm C: CAF 300/30/300; # of obese patients n = 190</td>
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Cockroft to evaluate GFR rate (Calvert formula using the Chatelut equation))

Endometrial cancer patients.

To compare a combination of cisplatin (30 mg/m2 on days 2 and 3).

NSCLC and/or wit carboplatin and cisplatin with ifosfamide for cervical, ovarian, endometrial cancer treated with CMF.

Chatelut: AUC <2.5, N=203, AUC >2.5

For analysis – 3 groups: Cisert AUC<1, N=137; AUC 1-6, N=260; AUC>6 N=99. Chatelut: AUC<2.5, N=203, AUC 2.5-6.5 N=151, AUC >6.5 N=142

Chatelut: AUC >3.5

To compare a combination of cisplatin and cyclophosphamide methotrexate

There was an excellent linear correlation between the different ways of measuring response. But with the Chatelut method the calculated administered AUC was lower. Notes: Whichever method was used, carboplatin AUC was not significantly associated with antitumour response rate nor patient survival. Whichever method was used to calculate the AUC and whether assessed continuously or categorised into three classes, there was no significant association between the carboplatin AUC dosage administered and the objective response rate. The results in terms of impact of the AUC on response rate, survival and toxicity were very similar.

Thrombocytopenia appeared to be significantly associated with the carboplatin AUC dose delivered. CC Leuopenia Grade 1

Efficacy

Toxicities

Conclusions

A higher proportion of obese patients (59% [97 of 249]) received less than 85% of protocol specified dose during the first course of CMF compared with patients with normal and intermediate BMI (14% [29 of 191]) (P=0.001).

Considering all patients together in analyses stratified by BMI group, reduced dose in the first cycle compared with protocol specified dose was associated with a significantly worse outcome for the ER negative or low ER tumors. Reduction in chemotherapy should be avoided.

For obese patients reducing the dose of chemotherapy was associated with a significantly worse outcome for the ER-negative cohort [total population hazard ratio = 8.5% vs 95% CI 0.83-0.85 [P=0.0001] for disease free survival; 0.72 [95% CI 0.56-0.94] for overall survival] but not for the ER-positive cohort [95% CI 1.16 [0.97-1.40] to 1.16 [95% CI 0.94-1.44] for overall survival] [interaction p value=0.0002 for disease free survival and =0.003 for overall survival].

They concluded that for a moderate carboplatin dose in non-small cell lung cancer, the therapeutic index could be improved if dosage is calculated according to the AUC.

With the Calvert Cockcroft method, the odds ratio for increased toxicity was OR 2.90 (P=0.001) in favour of the CC arm and OR 2.64 (P=0.001) in favour of low carboplatin AUC.

With the Cockcroft method, the OR was 2.50 (P=0.001) for the treatment arm and 2.35 (P=0.001) for the AUC dose.

With the Calvert Cockcroft method, the OR were, respectively, for treatment arm and AUC dose, 4.01 (P=0.0001) and 1.41 (P=0.001). With the Chatelut formula, they were, respectively, 3.98 (P<0.001) and 1.40 (P=0.001)

Obese patients initially treated with expected doses of chemotherapy (>95%) did not have more grade 3/4 toxicity than patients who received reduced (< 85%) doses (14% [22 of 152] vs 12 [12 of 97] respectively; P= 0.62).

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Obese patients initially treated with expected doses of chemotherapy (>95%) did not have more grade 3/4 toxicity than patients who received reduced (< 85%) doses (14% [22 of 152] vs 12 [12 of 97] respectively; P= 0.62).

They concluded that for a moderate carboplatin dose in non-small cell lung cancer, the therapeutic index could be improved if dosage is calculated according to the AUC.
To examine the effect of BSA and OS of parameters reflecting the body size, body weight and height, BMI, and BSA on the depth of the blood leukocyte nadir in breast cancer patients receiving adjuvant chemotherapy, when drug dosing was based on the BSA.

### Methods

**Chemotherapy:**

- Epirubicin: 12.5-120 mg/m²
  - N = 32
  
  Patients were treated with epirubicin 12.5-120 mg/m² given as a slow bolus intravenous injection. Treatment dose was selected by the clinician.

### Efficacy

There was no difference in the CV of adjusted and unadjusted clearance (39.4% and 37.7%, respectively). Patients with high BMI had higher leukocyte nadirs than lean patients (P = 0.3). High leukocyte nadirs also associated with high body weight and large BSA, but not height (refer to Table 2 for more details). Variation in depth of leukocyte nadir substantial even between patients with similar BMI. Despite adjusting for age and CYC dose, association between BMI and leukocyte nadir was still highly significant (P = 0.001).

High BMI associated with high leukocyte nadir in subgroup of patients who had all received similar mg dose of CYC (1000 to 1100 mg, n = 321, r = 0.25, P < 0.01)

Patients within the highest BMI had the highest leukocyte nadir values (P < 0.001). A high body weight and a large BSA were also associated with high leukocyte nadirs.

### Toxicities

No data

### Conclusions

When the blood leukocyte nadir is used as a surrogate marker for the drug effect, obese patients receiving intravenous CMF have higher leukocyte nadirs than the lean ones. Therefore, the drug doses should not be reduced because of obesity, and even when obese patients are treated according to the scheduled doses they may remain slightly underdosed.

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### Tables

#### Table 1

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| Dobbs, 1996  | To address questions in patients with advanced primary breast cancer: (1) do physical characteristics influence the variability in epirubicin pharmacokinetics? (2) does adjustment of dose according to surface area appear to reduce this variability? (3) what would be the effect on epirubicin pharmacokinetics and pharmacodynamics of abandoning surface area dose normalization? | **PK Study: Single Arm**
  - Chemotherapy: epirubicin 12.5-120 mg/m²
  - N = 32
  
  Patients were treated with epirubicin 12.5-120 mg/m² given as a slow bolus intravenous injection. Treatment dose was selected by the clinician. To reduce the possible bias of the older and less fit women being treated at lower doses, some of the younger patients were treated using divided doses. In these women the usual dose of epirubicin was given on day 1 and the remainder administered 48 h later. After completing pharmacokinetic sampling. These patients were excluded from the pharmacodynamic analysis of myelosuppression. Treatment continued on a 3-week schedule. | | | |

There was no association found between body weight, height, BMI, or BSA and DFS or OS (P > 0.1 for all comparisons). High leukocyte nadirs also associated with high body weight and large BSA, but not height (refer to Table 2 for more details). Variation in depth of leukocyte nadir substantial even between patients with similar BMI. Despite adjusting for age and CYC dose, association between BMI and leukocyte nadir was still highly significant (P = 0.001). Patients within the highest BMI had the highest leukocyte nadir values (P < 0.001). A high body weight and a large BSA were also associated with high leukocyte nadirs. | | |

#### Table 2

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  - N = 32
  
  Patients were treated with epirubicin 12.5-120 mg/m² given as a slow bolus intravenous injection. Treatment dose was selected by the clinician. To reduce the possible bias of the older and less fit women being treated at lower doses, some of the younger patients were treated using divided doses. In these women the usual dose of epirubicin was given on day 1 and the remainder administered 48 h later. After completing pharmacokinetic sampling. These patients were excluded from the pharmacodynamic analysis of myelosuppression. Treatment continued on a 3-week schedule. | | | |

There was no association found between body weight, height, BMI, or BSA and DFS or OS (P > 0.1 for all comparisons). High leukocyte nadirs also associated with high body weight and large BSA, but not height (refer to Table 2 for more details). Variation in depth of leukocyte nadir substantial even between patients with similar BMI. Despite adjusting for age and CYC dose, association between BMI and leukocyte nadir was still highly significant (P = 0.001). Patients within the highest BMI had the highest leukocyte nadir values (P < 0.001). A high body weight and a large BSA were also associated with high leukocyte nadirs. | | |

---

### Evidence

- **Single Arm**
  - Chemotherapy: epirubicin
  - N = 32

There was wide variability in both unadjusted epirubicin clearance (mean 49.5 ± 1 h⁻¹, range 17.7-91.7) and adjusted clearance (mean 30.5 ± 1 h⁻¹, range 13.1-58.0). There was a linear relationship between total epirubicin dose and AUC (r = 0.80, P < 0.001). The observed neutrophil nadir (r = 0.85, P < 0.001). This was reflected in the significantly higher AUC of the five patients with grade 3/4 neutropenia compared with the six with less severe myelosuppression (4363 and 1611 ng ml⁻¹ h respectively, P = 0.02 Mann-Whitney test).

Epirubicin AUC had the strongest relationship with both the absolute neutrophil nadir (r² = 0.72) and total WBC nadir (r² = 0.43). This relationship was stronger than that of epirubicin dose with neutrophil nadir or WBC nadir (r² = 0.51 and 0.47 respectively). Similarly, epirubicin AUC was the only parameter strongly associated with the surviving fraction of both neutrophils and total WBC (r² = 0.62 and 0.57 respectively).

### Conclusion

In 11/32 patients an analysis of actual and predicted neutropenia confirmed that unadjusted dosing would have had no significant effect on the pattern of myelosuppression.
<table>
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<tr>
<th>Author, Year</th>
<th>Objectives</th>
<th>Methods</th>
<th>Efficacy</th>
<th>Toxicities</th>
<th>Conclusions</th>
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</thead>
<tbody>
<tr>
<td>Gibbs, 1999</td>
<td>To measure oral clearance (CL/F, mL/min) of busulfan of cancer patients - Breast (ER/HER2 status and pre or post menopause) (n = 55); ovarian (n = 15); Leukemia: ALL (n = 42); CML (n = 73); MDS (n = 49); NHL (n = 10); Multiple Myeloma (n = 25)</td>
<td>PK study</td>
<td>Efficacy: To measure oral clearance (CL/F, mL/min) of busulfan of cancer patients - Breast (ER/HER2 status and pre or post menopause) (n = 55); ovarian (n = 15); Leukemia: ALL (n = 42); CML (n = 73); MDS (n = 49); NHL (n = 10); Multiple Myeloma (n = 25)</td>
<td>Toxicities: None specified</td>
<td>Conclusions: Data suggest that the apparent reduction in busulfan CL/F in NHL patients could result in enhanced toxicity after a fixed 1 mg/kg dose. However, the small number (n = 10) of NHL patients included in this analysis suggests that this issue should be investigated further. Busulfan CSS was related to regimen-related toxicity and graft rejection in 42 patients with a variety of diseases undergoing hematopoietic stem cell transplantation. Severe grade 3-4 RRT was only observed in patients with CSS &gt; 900 ng/mL. Routine dosing of oral busulfan on the basis of BSA or AIBW in adults and adolescents does not require a specific accommodation for the obese. However, dosing based on BSA may be improved by considering CL/F differences in certain diseases. Adjusting dose for body size or disease does not diminish interpatient variability sufficiently to obviate plasma level monitoring in many indications. In conclusion, absolute busulfan CL/F is elevated in obesity. There appears to be a potentially important difference between NHL patients and those with NHL in busulfan CL/F expressed relative to BW, BSA, or AIBW. Even when expressed relative to BSA or AIBW, interpatient variability in busulfan CL/F expressed relative to any measure of body size is large relative to the therapeutic window in certain indications. The need for adjusting busulfan dose based on AUC or CSS measured in the individual patient remains in certain settings regardless of body size measure.</td>
</tr>
<tr>
<td>Mathijssen, 2002</td>
<td>To evaluate relationships between various body-size measures and irinotecan clearance and metabolism in cancer patients, and to provide future dosing recommendations for this agent.</td>
<td>PK Study - Phase II</td>
<td>Efficacy: The mean irinotecan clearance was 33.6 ± 10.8 L/h, with an interindividual variability of 32.1%. Significant differences in mean busulfan CL/F expressed relative to BW were found in patients with NHL, in comparison to those with CML (B7.9 ± 12.3 vs 16 ± 25 mL/min/m2, P &lt; .006, respectively). The mean CL/F expressed relative to ABW was statistically significantly different in patients with NHL compared with those with BCA (2.41 ± 0.42 vs 1.35 ± 0.82 mL/min/kg, P &lt; .012, respectively), NHL &lt; CML (2.41 ± 0.42 vs 2.20 ± 0.70 mL/min/kg, P &lt; .006, respectively), and NHL &lt; MM (2.41 ± 0.42 vs 2.24 ± 0.61 mL/min/kg, P &lt; .012, respectively).</td>
<td>Toxicities: None specified</td>
<td>Conclusions: The nonscientifically based BSA-based dosing strategy should be replaced by alternative strategies. Despite the lack of basic fundamentals, BSA-based dosing still seems “untouchable” in clinical oncology.</td>
</tr>
</tbody>
</table>

Mathijssen, 2002

To evaluate relationships between various body-size measures and irinotecan clearance and metabolism in cancer patients, and to provide future dosing recommendations for this agent.

**PK Study - Phase II**

**Chemotherapy:** Irinotecan @90-minute IV infusion (dose range, 175 to 350 mg/m²)

**N=82 patients**

**Efficacy:** The mean irinotecan clearance was 33.6 ± 10.8 L/h, with an interindividual variability of 32.1%. When clearance was adjusted for BSA, the interindividual variability was similar at 34.0%.

**Toxicities:** No data

**Conclusions:** The nonscientifically based BSA-based dosing strategy should be replaced by alternative strategies. Despite the lack of basic fundamentals, BSA-based dosing still seems “untouchable” in clinical oncology.
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<tr>
<td>Miller, Rudek, 2004</td>
<td>To explore the influence of age, body size, concomitant drugs, dose, infusion duration, and sex on the clearance for doxorubicin and docetaxel in patients malignant solid tumors.</td>
<td>PK Study - Single Arm</td>
<td>Chemotherapy: doxorubicin [Taxol] doxorubicin [Adriamycin] N=243 (Dox N=110; Doc N=152); 19 patients received both doxorubicin and docetaxel in combination therapy Arm A: Dox N=110 Arm B: Dox N= 152 Doc and Doc N=152 (excluded from analysis)</td>
<td>The mean clearance was 63.6 ± 22.7 L/h for doxorubicin and 42.8 ± 14.9 L/h for docetaxel, Normalisation BSA reduced the interindividual variability by only &lt;1.7%. Doxorubicin clearance was significantly reduced when administered at doses &gt;50 mg/m2 in combination with cyclophosphamide. Upper extremes of body size were associated with increased clearance for both drugs, whereas no consistent effect of age on clearance was discerned. Arm A: A positive association was observed between BSA and doxorubicin clearance (r=0.34; P=0.002); a separate analysis in males and females revealed a stronger correlation in males (r=0.64; P=0.0002) than females (r=0.21; P=0.39). Clearance was 22% higher in patients with BMI &gt; 30 kg/m2 (63.6 ± 19.9 L/h versus 55.7 ± 17.1 L/h; P=0.041). No sex differences found. Arm B: The mean plasma clearance of docetaxel was 42.8 ± 14.9 L/h (range 13.8-84.4 L/h) with a CV of 34.8%, and was similar among the different drug administration schedules (P=0.16). A positive correlation was noted between BSA and doxorubicin clearance (r=0.30; P=0.002); a separate analysis revealed a stronger correlation in males (r=0.55; P=0.002) than in females (r=0.28; P=0.11). Clearance was not higher in patients with BMI &gt; 30 kg/m2 (40.9 ± 13.1 L/h versus 46.1 ± 13.5 L/h; P=0.15). Docetaxel clearance was reduced on average by 11% in females compared to males (40.6 ± 14.7 L/h versus 45.6 ± 14.8 L/h; P=0.040). No sex differences were found.</td>
<td>The mean clearance was 8 ± 14.9 L/h for docetaxel. The limited sampling strategy used for T &gt; 0.05 umol/L had a mean error of 0.67% and root mean squared error of 5.6%. The limited sampling strategy used for T &gt; 0.05 umol/L was T &gt;0.05 umol/L. No data</td>
</tr>
<tr>
<td>Niles, Renton, 2004</td>
<td>To study a fixed dose (360 mg) of paclitaxel given i.v. over 3 hours to female patients, and to evaluate prospectively the relationships between the following: BSA and toxicity; BSA and pharmacokinetics; and pharmacokinetics and toxicity.</td>
<td>PE Study - Single Arm</td>
<td>Chemotherapy: paclitaxel [Taxol] N=32 The dose normalized for body surface area ranged from 162 to 300 mg/m2. Estimation of area under the concentration versus time curve (area under the curve) used a limited sampling strategy by which AUC (umol/L-h) was calculated from the following equation: area under the curve = concentration at 3 hour + 10 (concentration at 6 hours) +0.63. The limited sampling strategy used for area under the curve had a mean error (reflecting bias) of 3.2% and root mean squared error (representing precision) of 9.8%. The limited sampling strategy used for T &gt; 0.05 umol/L was T &gt;0.05 umol/L. No data. Paclitaxel pharmacokinetics were assessed in the first cycle of treatment only. Four blood samples were obtained: before the paclitaxel infusion; and at 1, 4, and 24 hours from the start of the 3-hour infusion. The total (not free) paclitaxel concentrations were measured by high performance liquid chromatography. Total body clearance was calculated from the relationship as follows: clearance = dose / area under the curve.</td>
<td>The median BSA for both studies was approximately the same. The actual doses given to patients in CALGB 9342 varied widely around the median of 370 mg (Table 2). The median calculated dose of 210 mg/m2 on CALGB 9763 was only slightly less than the dose of 210 mg/m2 used on CALGB 9422. The toxicity profiles for the two studies were similar. BSA was inversely correlated with area under the curve (r = 0.07; P = 0.005) and correlated with total body clearance (r = 0.07; P = 0.005), but BSA was not correlated with total clearance &gt; 0.05 umol/L (r = 0.03; P = 0.19). The limited sampling strategy used a limited sampling strategy. A positive association was observed between BSA and doxorubicin clearance (r=0.34; P=0.002); a separate analysis in males and females revealed a stronger correlation in males (r=0.64; P=0.0002) than females (r=0.21; P=0.39). Clearance was 22% higher in patients with BMI &gt; 30 kg/m2 (63.6 ± 19.9 L/h versus 55.7 ± 17.1 L/h; P=0.041). No sex differences found. Docetaxel clearance was reduced on average by 11% in females compared to males (40.6 ± 14.7 L/h versus 45.6 ± 14.8 L/h; P=0.040). No sex differences were found.</td>
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</tr>
</tbody>
</table>
To evaluate prospectively (multi-center study) the benefit of using cystatin C levels (as a marker for GFR) for carboplatin individual dosing for patients with primary ovarian (N=150), uterine (N=44), head and neck (N=15), lung (N=36) and other (N=108).

**PK Study - Single Arm**

**Chemotherapy:** Carboplatin as single agent (N=90) Carboplatin with other agents N=278 5 FU (N=7) doxorubicin (N=9) docetaxel (N=9) etoposide (N=15) gemcitabine (N=17) paclitaxel (N=234) vinorelbine (N=10) other (N=11)

N=357 patients included in this study were receiving carboplatin as a part of established protocols.

Seven covariates studied were as follows Scr, cyst(C, age, sex, BMI): ideal body weight, and lean body mass.

The best covariate equation was: carboplatin clearance (mL/min/1.73 m²) = 117.8 * (Scr/75) * 0.847 * (age/56) * 0.450 * (sex).

Using an alternative weight descriptor (ideal body weight or lean body mass) did not improve the prediction. The final covariate model was validated by bootstrap analysis. The bias (mean percentage error) and imprecision (mean absolute percentage error) were +1% and +15% respectively, on the total population, and were of similar magnitude in each of the three subgroups of patients defined according to their body mass index. The observed R² of total paclitaxel were similar in both dosing groups, with mean values 0.80 (A) vs 0.82 (B), 0.82 (A) vs 0.83 (B), and lean body mass (r = 0.80; P = 0.028).

The exposure to unbound paclitaxel, total paclitaxel, and Cremophor EL was similar in both dose groups (BSA-based dose v flat fixed dose), with overall mean AUC values of 1.34 ± 0.16 vs 1.30 ± 0.33 uM/h; P = 0.63, 17.7 ± 3.0 vs 17.3 ± 5.2 uM/h; P = 0.71 and 57 ± 13.9 vs 55.5 ± 17.7 uM/h; P = 0.53, respectively.

The absolute clearance of cisplatin, paclitaxel, and troxacitabine was significantly increased in the obese (P < 0.023), but BMI was not observed for carboplatin, docetaxel, irinotecan, or topotecan (P > 0.17). For doxorubicin, the systemic exposure was significantly reduced in obese women (P = 0.013), but not in obese men (P = 0.52). Evaluation of alternate weight descriptors for dose calculation in the obese, including predicted normal weight, lean body mass, (adjusted) ideal body weight descriptors for dose calculation in the obese patients, including a priori dose reduction or dose capping, should be discouraged.

**Toxicities**

None of the patients developed grade 2 or greater nonhematologic toxicity, and there were no episodes of neutropenic fever or treatment-related deaths. Overall, hematologic toxicity in the first cycle was mild.

This study indicates that paclitaxel disposition is significantly related to BSA. This provides a pharmacokinetic rationale for BSA based dosing of this drug.

The absolute clearances of unbound and total paclitaxel were significantly related to various measures of body size, except for height. The observed R² values indicate that BSA explains around 38% of the total variation in clearance of unbound paclitaxel and around 65% of the total variation in clearance of total paclitaxel. These values are similar to the percentage of total variation explained by weight, so weight is probably the more important factor in explaining the variation in paclitaxel clearance.

The results suggest that a number of widely used empiric strategies for dose adjustments in obese patients, including a priori dose reduction or dose capping, should be discouraged.

**Conclusions**

Individual dosing of carboplatin is a current practice to control plasma drug exposure of this drug. The main limitation of the existing equations is that they are all based on serum creatinine level as the unique biological covariate; it has been shown that these formulae overestimate carboplatin clearance in obese patients.

For the first time, a unique formula (Modified Thomas) is proposed for carboplatin individual dosing to patients, which is shown to be equally valid for underweight, normal weight, and obese patients.
**Author, Year**  
Okamoto, 1998

**Objectives**  
To evaluate the performance of the three formula (Calvert, Cockcroft-Gault, Chatelut) in predicting standard- and low-dose carboplatin pharmacokinetics for patients with locally advanced NSCLC (N=25), SCLC (N=20), Metastatic NSCLC or recurrent SCLC (N=7)

**Methods**  
PK Study - Single Arm  
Chemotherapy: carboplatin - standard dose (N=27) and low-dose (N=25)

- Arm A (N=27): standard-dose of carboplatin  
- Arm B (N=25): low-dose carboplatin (25mg/m², i.v.)

**Efficacy**  
Result Arm A: MAPEs for the prediction of carboplatin CL from the 24-h Calvert, CG-Calvert and Chatelut formulae were 13%, 12% and 23%, respectively

Result Arm B: MAPEs were 27%, 18% and 44%, respectively.

**Toxicities**  
Observed standard-dose carboplatin AUCs after aiming for target AUCs of 5 and 6 mg x min/ml using the Calvert formula based upon the 24-h Ccr were 5.3 ± 0.8 and 5.9 ± 0.8, respectively, indicating a small and acceptable bias compared with that predicted from the dosing formula.

**Conclusions**  
The pharmacokinetics of standard-dose carboplatin were accurately predicted by the Calvert formula based upon either 24-h or CG-calculated Ccr, but not by the Chatelut formula. Either CG-calculated or 24-h Ccr can be substituted for the GFR in the Calvert formula for the determination of individual doses. The poor predictability of the Chatelut formula found in this study might be the result of a differences in either the Cr assay or the patient population. Therefore, formulae which attempt to estimate GFR are not necessarily valid if either the Cr assay or the patient population is changed.

**Author, Year**  
Ekhart, 2009

**Objectives**  
To determine the utility of alternative weight descriptors in the Cockcroft-Gault equation to more accurately predict carboplatin clearance in patients with many cancers.

**Methods**  
Retrospective cohort  
Clearance values were obtained from individual fits using NONMEM and were compared to predicted carboplatin clearances calculated with the Cockcroft-Gault equation using diverse weight descriptors

Chemotherapy:  
- PC: Paclitaxel and carboplatin  
- CTC: Carboplatin and high dose cyclophosphamide (1 h infusion) and thiotepa (2 x 0.5h infusion every day for 4 days)  
- miniCTC: day 1 Carboplatin and cyclophosphamide (1 h infusion), day 2 thiotepa 1 h infusion of carboplatin and thiotepa

Notes: NSCLC PC dose carb 300-400 mg/m² per min; NSCLC 2-6 PC (dose carb AUC 6 mg min/mL administered in 30 min); High risk primary breast (dose carb AUC 400 mg/m² per day or AUC 20 mg min/mL administered in 1 h for 4 days); germ cell CTC (dose carb 400 mg/m²/day or AUC 20 mg min/mL administered in 1 h for 4 days); Metastatic ovarian CTC (dose carb 267 mg/m² per day or AUC 13.5 mg min/mL administered in 1 h for 4 days); Epithelial breast mini CTC (dose carb 400 mg/m² per day or AUC 10 mg min/mL administered in 3 h for 2 days)

N= 240 patients with 380 chemotherapy courses and 4478 samples

**Efficacy**  
In overweight and obese patients with normal renal function a flat carboplatin dose should be administered based on the population carboplatin clearance (8.38l/h=140L/min). In the case an AUC of 5 mg min/mL is desired, the appropriate dose for carboplatin would be 5 x 140-700 mg.

Results suggest that a flat dose carboplatin = target AUC x carboplatin clearance) based on the population carboplatin clearance (8.38l/h=140 mL/min) will result in less bias in overweight and obese patients with adequate renal function.

**Toxicities**  
In overweight and obese patients with a normal renal function, a flat carboplatin dose should be administered based on the population carboplatin clearance (8.38l/h=140 mL/min). In the case of an AUC of 5 mg min/mL is desired, the appropriate dose for carboplatin would be 5 x 140-170 mg.

**Conclusions**  
Incorporation of allometric coefficient (range 18.5-18.8%) did not significantly improve the fit of the model (differences in GOF were less than 6.63) compared to the basic model (19.4%) in which no relation between weight and carboplatin clearance was assumed.
<table>
<thead>
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</table>

Key: 5 FU - 5-Fluorouracil; ABW - actual body weight; AC - doxorubicin and cyclophosphamide; BMI – body mass index; CAF - cyclophosphamide, doxorubicin, and fluorouracil; CCI – Charlson comorbidity index; CHOP- cyclophosphamide, doxorubicin, vincristine, and prednisone; CHOP-R-CHOP rituximab; CNOP- cyclophosphamide, mitoxantrone, vincristine, and prednisone; (CL/V, Ml/min) – oral clearance; CSF – colony stimulating factor; (cysC) – cystatin C level; CV - coefficient of variation; EBC – early breast cancer; FL – grade II neuropathy; GFR – glomerular filtration rate; GOG – Gynecologic Oncology Group; IBW- ideal body weight; I.V - intravenously; MAPE – median absolute percent error; NSCLC- non-small cell lung cancer; OS – overall survival; pCR- pathological complete response; PFS – progression-free survival; PK – Pharmacokinetic; PS – performance status; RT – radiation therapy; RDI – reduced relative dose-intensity; RR – relative risk; SCLC - small cell lung cancer; SCT – stem cell transplant; SCRT – Severe chemotherapy related toxicity; Scr – serum creatinine level; Thal – Thalidomide; TTP – Time to Progression; WHO – World Health Organization; Vss – volume of distribution;
Data Supplement 3: Search strategy

Original search


Supplemental search

(("body surface area"[MeSH Terms] OR ("body"[All Fields] AND "surface"[All Fields] AND "area"[All Fields]) OR "body surface area"[All Fields]) AND dosing[All Fields]) AND ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields])
Data Supplement 4: Quorum Diagram: Exclusions and Inclusions of Publications Identified for Systematic Review

Potentially relevant abstracts identified by electronic searching and screened for retrieval

(n = 913)

Articles retrieved for full text review

(n=148)

Articles that met selection criteria for data extraction

(n=56)

Articles excluded after full text review

(n=767)

Additional articles recommended by Panel members or identified by hand-searching

(n=8 on morbidly obese, excluded)

(n= 4 other papers, excluded)

Articles excluded after full text review

(n=92)

Articles excluded after full text review

(n=92)
Data Supplement 5: Glossary and BSA Formulas

**Pharmacokinetics** is the study of the action of drugs within the body, which can, in many respects, be envisioned more accurately as the actions of the body on an administered drug. It includes studies of the mechanisms of drug absorption, distribution, metabolism, and excretion; onset of action; duration of effect; biotransformation; and effects and routes of excretion of the metabolites of the drug. Pharmacokinetics can be referred to as "PK".

**Pharmacodynamics** is the study of the physiological effects of drugs on the body or on microorganisms or parasites within or on the body and the mechanisms of drug action and the relationship between drug concentration and effect. One dominant example is drug-receptor interactions as modeled by

\[ L + R \rightleftharpoons L \cdot R \]

where \( L \) = ligand (drug), \( R \) = receptor (attachment site), reaction dynamics that can be studied mathematically. Pharmacodynamics can be referred to as “PD”.

**PKPD**

In conjunction with pharmacokinetics, pharmacodynamics can be referred to as "PKPD".


General definitions that apply across all adverse events (AE), with the caveat that “Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for grade selection.

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL).

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to AE.
Calculation Tools for Body Surface Area (BSA) and Body Mass Index (BMI)

Chemotherapy is usually dosed by square meter of body surface area (BSA). BSA has been chosen rather than body weight as the basis for calculation for two reasons. First, BSA has been demonstrated to provide a more accurate comparison of activity and toxicity for certain drugs. Second, BSA can be more closely correlated with cardiac output, which determines the blood flow to the liver and kidneys, thus influencing drug elimination.

Common Formulae – most did incorporate sex and none were developed in a typical 21st century population. ASCO does not endorse any particular calculator.

Carboplatin Calculation Resource

Calvert Formula - [https://hccapps.musc.edu/hemonc/carboplatin_dose_calculator.htm](https://hccapps.musc.edu/hemonc/carboplatin_dose_calculator.htm)

Total Dose (mg) = (target AUC) X (GFR + 25)

BSA Calculation Resources


BSA (m²) = 0.0003207 x Ht (cm)⁰.³ x weight (g)⁰.⁷₂₈₅ - ( ⁰.₀₁₈₈ x LOG(grams) )

Based on 197 patients


BSA(m²) = Wt(kg)⁰.₄₂₅ x Ht(cm)⁰.₇₂₅ x 0.007184

This is the classic formula, published in 1916, on which many monograms are based. However, it was based on measurements of 9 individuals, one of whom was a child.


BSA(m²) = Wt(kg)⁰.₅₁₄₅₆ x Ht(cm)⁰.₄₂₂₄₆ x 0.0235

This formula is based on direct measurements of 401 individuals.


\[
\text{BSA}(m^2) = Wt(kg)^{0.5378} \times Ht(cm)^{0.3964} \times 0.024265
\]

Haycock et al. reported that the formula of DuBois and DuBois increasingly underestimated BSA as values fell below 0.7 \(m^2\). Their formula was based on measurements of 81 individuals ranging from premature infants to adults.


\[
\text{BSA} \left( m^2 \right) = \frac{\text{Ht (cm)} \times \text{Wt (kg)}}{3600} \quad \text{or} \quad \frac{\text{Ht (in)} \times \text{Wt (lb)}}{3131}
\]

This formula is a simple modification of an equation by Gehan and George, and requires the use of a calculator with a square root key. The formula has been confirmed as being applicable to children by Lam and Leung. (SQR RT = Square Root of…)

Data Supplement 6: Interpretation of BMI for adults

For adults 20 years old and older, BMI is interpreted using standard weight status categories that are the same for all ages and for both men and women. For children and teens, on the other hand, the interpretation of BMI is both age- and sex-specific. For more information about interpretation for children and teens, visit Child and Teen BMI Calculator.

Calculation of BMI
For adults 20 years old and older, BMI is interpreted using standard weight status categories that are the same for all ages and for both men and women. For children and teens, on the other hand, the interpretation of BMI is both age- and sex-specific. For more information about interpretation for children and teens, visit Child and Teen BMI Calculator.

BMI is calculated the same way for both adults and children. The calculation is based on the following formulas:

<table>
<thead>
<tr>
<th>Measurement Units</th>
<th>Formula and Calculation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kilograms and meters (or centimeters)</strong></td>
<td>Formula: weight (kg) / [height (m)]^2</td>
</tr>
<tr>
<td></td>
<td>With the metric system, the formula for BMI is weight in kilograms divided by height in meters squared. Since height is commonly measured in centimeters, divide height in centimeters by 100 to obtain height in meters.</td>
</tr>
<tr>
<td></td>
<td>Example: Weight = 68 kg, Height = 165 cm (1.65 m)</td>
</tr>
<tr>
<td></td>
<td>Calculation: 68 ÷ (1.65)^2 = 24.98</td>
</tr>
<tr>
<td><strong>Pounds and inches</strong></td>
<td>Formula: weight (lb) / [height (in)]^2 x 703</td>
</tr>
<tr>
<td></td>
<td>Calculate BMI by dividing weight in pounds (lbs) by height in inches (in) squared and multiplying by a conversion factor of 703.</td>
</tr>
<tr>
<td></td>
<td>Example: Weight = 150 lbs, Height = 5'5&quot; (65&quot;)</td>
</tr>
<tr>
<td></td>
<td>Calculation: [150 ÷ (65)^2] x 703 = 24.96</td>
</tr>
</tbody>
</table>