various drugs and in the expression of drug-catabolizing enzymes, that is, cytochromes, in the elderly. Although old age appears not to have an effect on the pharmacokinetics of most drugs, the examples set forth by Shah (147) provide a concrete basis for establishing the elderly as a subgroup, or in excluding the elderly, when designing clinical trials.

According to the ICH Guidelines on geriatrics (148), "[t]he geriatric population is arbitrarily defined, for the purpose of this guideline, as comprising patients aged 65 years or older. It is important, however, to seek patients in the older age range, 75 and above, to the extent possible. Protocols should not ordinarily include arbitrary upper age cutoffs." Moreover, the ICH Guidelines provide the advice that, "[p]atients entering clinical trials should be reasonably representative of the population that will be later treated by the drug" (149), and further warn that, "[i]t is important to determine whether or not the pharmacokinetic behavior of the drug in elderly subjects or patients is different from that in younger adults and to characterize the effects of influences, such as abnormal renal or hepatic function, that are more common in the elderly" (150).

c. Subgroup of Subjects with No Metastasis and Subgroup of Subjects with Metastasis

The oncology trial of Grier et al. (151) included two study arms, as indicated:

- *Arm A*. Standard drugs.
- *Arm B*. Standard drugs plus two other drugs, ifosfamide and etopside.

The study population was stratified into two subgroups. The two subgroups were patients with metastasis (at baseline) and those without metastasis (at baseline). The results demonstrated no difference between arm A and arm B, with analysis of the subgroup having metastasis at baseline. However, the results demonstrated a striking and dramatic difference in efficacy in the arm B group, for the subgroup having no metastasis at baseline. To view the data, one of the endpoints was that of 5-year overall survival. Five-year overall survival refers to the percent of all of the subjects, for a given study arm, still alive at the 5-year time point. For the subgroup of non-metastatic subjects, the value for 5-year overall survival for the standard therapy group was 61%, while that for the experimental group was greater, 71% ($P = 0.01$). But for the subgroup of metastatic subjects, no significant difference in 5-year overall survival was detected between the two study arms—there was a slight difference, but this difference was not significant ($P = 0.81$). P values are explained further in this textbook in Chapter 9.

This result is concrete and easy to put into practice in the context of routine patient care. In other words, it is a routine task to determine whether a patient's cancer is metastatic, and to provide the appropriate drugs.

[147]Shah RR. Drug development and use in the elderly: search for the right dose and dosing regimen (Parts I and II). Br. J. Clin. Pharmacol. 2004;58:452–69.

[148]ICH Harmonised Tripartite Guideline. Studies in support of special populations:geriatrics. Step 4 version, June 1993, 4 pages.

[149]ICH Harmonised Tripartite Guideline. Studies in support of special populations:geriatrics. Step 4 version, June 1993, 4 pages.

[150]ICH Harmonised Tripartite Guideline. Studies in support of special populations:geriatrics. Step 4 version, June 1993, 4 pages.

[151]Grier HE, Krailo MD, Tarbell NJ, et al. Addition of ifosfamide and etoposide to standard chemotherapy for Ewing's sarcoma and primitive neuroectodermal tumor of bone. N. Engl. J. Med. 2003;348:694–701.