Therapeutic Index and Its Clinical Significance

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- The main purpose of delivering radiotherapy is to cure the disease with no or minimal normal tissue complications. An ideal radiotherapy plan should have a 100% chance of curing the disease while there is 0% chance of normal tissue complications which never occur. But in reality normal tissues undergo significant dammage by the dose required to control the tumor; while the tumor may not receive an adequate dose if the 100% normal tissue protection is planned.
- When we plot a graph of probability of tumor control in Y axis against radiation dose in X axis what we get is the tumor control probability (TCP). Similarly when probability of normal tissue complications in Y axis is plotted against radiation dose in X axis we get the normal tissue complication probability (NTCP) [1]. TCP and NTCP curves are sigmoid in shape. The therapeutic index (TI) defines how the TCP relates to NTCP for different doses of radiation (Fig. 31.1).
- TI = NTCP/TCP
- Usually radiosensitive tumors like seminoma have a wide therapeutic index, while those with radioresistant tumors have a narrow therapeutic index (Fig. 31.2).
- The therapeutic index for a particular tumor may also depend on the location of tumor, e.g., a soft tissue sarcoma of the extremity may have a good therapeutic index, while a retroperitoneal sarcoma located near to kidneys will have a very unfavorable therapeutic index.
- Dose volume histograms created in conformal radiotherapy plans and TCP and will help clinicians during treatment planning.
- An ideal radiotherapy plan where there is 100% chance of tumor control and 0% chance of normal tissue toxicity never really exists in real world scenario. Achieving an optimal balance between TCP and NTCP is a basic aim of any radiotherapy plan. This can be achieved

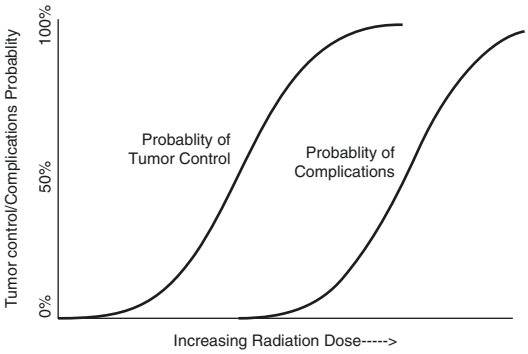

Fig. 31.1 Diagram showing concept of therapeutic index

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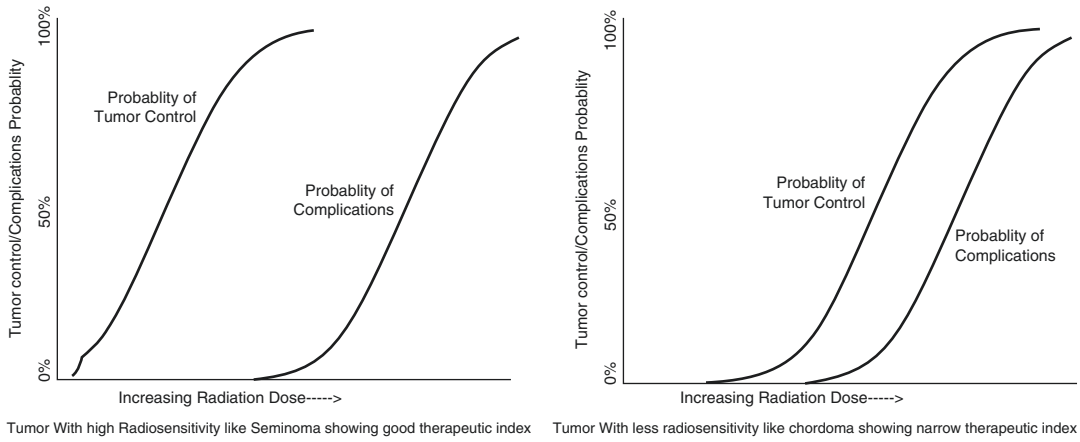

Fig. 31.2 Therapeutic index for radiosensitive and radioresistant tumors

by altering the radiation fractionation or radiation sensitizers or radiation protectors.

31.1 Modifying Therapeutic Index for Clinical Advantage

Modifying therapeutic index is the main advantage of adding chemotherapy or radiation sensitizers or radio protectors.

1. Hyperfractionation—In hyperfractionation small dose per fraction with two or three fraction delivered per day is used to achieve a higher biologically effective dose to the tumor. Using the lower dose per fraction also reduces the chances of long term normal tissue complications (shifting the NTCP to right), thereby improving the therapeutic index.
2. The therapeutic index is improved by reducing the size of the target volume and the margins by using image guidance in radiotherapy planning [2].
3. Concurrent Chemotherapy—The use of concurrent chemotherapy acts as a radiosensitizer and thereby shifts the TCP to left, thus improving therapeutic ratio. The nonoverlapping toxicity with concurrent chemotherapy (some overlapping toxicity exists like mucositis with concurrent cisplatin) does not greatly alter the NTCP.
4. Radiation Sensitizers—The use of radiosensitizers helps in optimizing therapeutic index by overcoming hypoxia. This can be achieved either by use of agents like nimorazole which is a hypoxic cell sensitizer or by administration of agents that are preferentially cytotoxic to hypoxic tumor cells (e.g., hyperthermia). This leads to shifting of TCP curves to the left, thereby improving therapeutic index.
5. Radio Protectors—The radio protectors (e.g., Amifostine) mainly act by neutralizing free radicals generated by ionizing radiations in the normal tissue, thereby reducing normal tissue complication rates [3]. Thus this leads to shifting of NTCP curves to the right, thereby improving therapeutic index.
6. Extracorporeal radiotherapy where tumor tissue is removed and the bone is irradiated outside the body may be one of the radiotherapy plans where we may archive something near to an ideal therapeutic index.

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