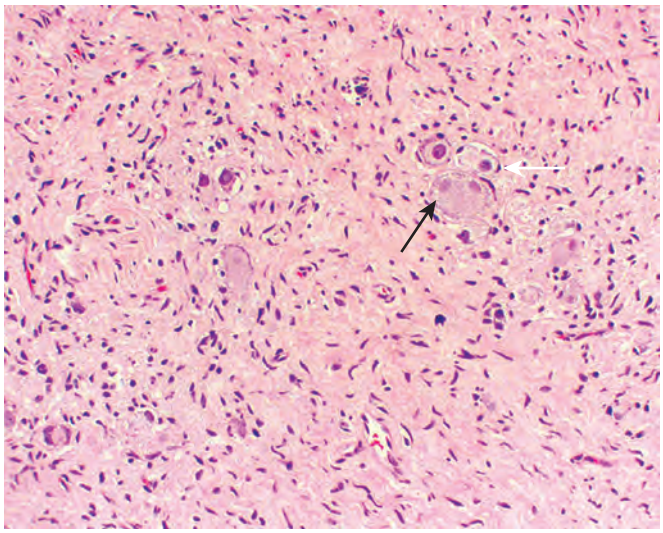

Figure 10-26 Ganglioneuromas, arising from spontaneous or therapy-induced maturation of neuroblastomas, are characterized by clusters of large cells with vesicular nuclei and abundant eosinophilic cytoplasm, representing neoplastic ganglion cells *(arrow)*. Spindle-shaped Schwann cells are present in the background stroma.

large cells resembling mature ganglion cells with few if any residual neuroblasts; such neoplasms merit the designation **ganglioneuroma** (Fig. 10-26). Maturation of neuroblasts into ganglion cells is usually accompanied by the appearance of **Schwann cells**. In fact, the presence of a so-called schwannian stroma composed of organized fascicles of neuritic processes, mature Schwann cells, and fibroblasts is a histologic prerequisite for the designation of ganglioneuroblastoma and ganglioneuroma; ganglion cells in and of themselves do not fulfill the criteria for maturation. The origin of Schwann cells in neuroblastoma remains an issue of contention; some investigators believe they represent a reactive population recruited by the tumor cells. However, studies using microdissection techniques have demonstrated that the Schwann cells harbor at least a subset of the same genetic alterations found in neuroblasts, and therefore are a component of the malignant clone. Irrespective of histogenesis, documenting the presence of schwannian stroma is essential, because its presence is associated with a **favorable outcome** (Table 10-8).

Metastases, when they develop, appear early and widely. In addition to local infiltration and lymph node spread, there is a pronounced tendency to spread through the bloodstream to the liver, lungs, bone marrow, and bones.

Staging. The International Neuroblastoma Staging System, which is the most widely used staging scheme worldwide, is detailed here:

- **Stage 1:** Localized tumor with complete gross excision, with or without microscopic residual disease; representative ipsilateral nonadherent lymph nodes negative for tumor (nodes adherent to the primary tumor may be positive for tumor).
- **Stage 2A:** Localized tumor with incomplete gross resection; representative ipsilateral nonadherent lymph nodes negative for tumor microscopically.
- **Stage 2B:** Localized tumor with or without complete gross excision; ipsilateral nonadherent lymph nodes positive for tumor; enlarged contralateral lymph nodes, which are negative for tumor microscopically.
- **Stage 3:** Unresectable unilateral tumor infiltrating across the midline with or without regional lymph node involvement; or localized unilateral tumor with contralateral regional lymph node involvement.
- **Stage 4:** Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, and/or other organs *(except as defined for stage 4S).*
- **Stage 4S** ("S" = special): Localized primary tumor (as defined for stages 1, 2A, or 2B) with dissemination limited to skin, liver, and/or bone marrow; *stage 4S is limited to infants younger than 1 year.*

Unfortunately, most (60% to 80%) children present with stage 3 or 4 tumors, and only 20% to 40% present with stage 1, 2A, 2B, or 4S neuroblastomas. The staging system is of paramount importance in determining prognosis.

Clinical Course and Prognostic Features. In young children, under age 2 years, neuroblastomas generally present with large abdominal masses, fever, and possibly weight loss. In older children, they may not come to attention until metastases produce manifestations, such as bone pain, respiratory symptoms, or gastrointestinal complaints. Neuroblastomas may metastasize widely through the hematogenous and lymphatic systems, particularly to liver, lungs, bones, and bone marrow. Proptosis and ecchymosis may also be present, due to spread to the periorbital region, a common metastatic site. Bladder and bowel dysfunction may be caused by paraspinal neuroblastomas that impinge on nerves. In neonates, disseminated neuroblastomas may present with multiple cutaneous metastases

Table 10-8 Prognostic Factors in Neuroblastomas

Variable	Favorable	Unfavorable
Stage*	Stage 1, 2A, 2B, 4S	Stage 3, 4
Age*	<18 months	>18 months
Histology*		
Evidence of schwannian stroma and gangliocytic differentiation†	Present	Absent
Mitosis-karyorrhexis index‡	<200/5000 cells	>200/5000 cells
DNA ploidy*	Hyperdiploid (whole chromosomal gains)	Near-diploid (Segmental chromosomal losses; chromothripsis)
*MYCN**	Not amplified	Amplified
Chromosome 1p loss	Absent	Present
Chromosome 11q loss	Absent	Present
TRKA expression	Present	Absent
TRKB expression	Absent	Present
Mutations of neuritogenesis genes	Absent	Present

*Corresponds to the most commonly used parameters in clinical practice for assessment of prognosis and risk stratification.
†It is not only the presence but also the amount of schwannian stroma that confers the designation of a favorable histology. At least *50% or more schwannian stroma* is required before a neoplasm can be classified as ganglioneuroblastoma or ganglioneuroma.
‡Mitotic karyorrhexis index (MKI) is defined as the number of mitotic or karyorrhectic cells per 5000 tumor cells in random foci.